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ANNALS OF
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THE ALARM REACTION AND THE DISEASES OF ADAPTATION *

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IN a lecture such as this it would be impossible to review the rather voluminous literature on the adaptation syndrome and the diseases of adaptation, but this is hardly necessary in any case because several extensive surveys of this field have been published in recent years (Albright, 1942–43; Albright, 1943; De La Balze, 1946; Cannon, 1932; Crile and Lower, 1915; Ingle, 1942; Laflaquière, 1942; Leblond, 1939; Maitre, 1942; Overbeek, 1947; Selye, 1940; Selye, 1941; Selye, 1944; Selye, 1946; Sundstroem and Michaels, 1942; Tepperman, Engel and Long, 1943; Varangot, 1940).

Since apparently one of the most important diseases of adaptation is hypertensive disease—especially the so-called "renal hypertension"—it would be well to discuss the pertinent literature, but here again the limitations of space force me merely to refer the reader to the most useful relevant reviews (Braun-Menendez, Fasciolo, Leloir, Munoz and Taquini, 1943; Braun-Menendez, Fasciolo, Leloir, Munoz and Taquini, 1946; Carrière and Huriez, 1936; Dumont, 1946; Fishberg, 1939; Gallaverdin, 1920; Goldring and Chasis, 1944; Goldring et al., 1946; Hueper, 1944–45; Lichtwitz, 1942; Page and Corcoran, 1945; Trueta, 1947; Viersma, 1946) and particularly to a synopsis of this field which I recently gave in my textbook (Selye, 1947). Here I should merely like to summarize the concept of the Diseases of Adaptation and to survey especially the more recent observations which support it. Perhaps it will help to follow a concise description of pertinent observations if we first outline the theories which we intend to illustrate with them. It must be stated at the onset that certain links in the chain of events which we believe to be responsible for the Diseases of Adaptation have not yet been fully proved and others may have to be replaced in the future, but wherever uncertainty exists, we shall emphasize the gaps in our knowledge.

*The essence of this paper was presented before the American College of Physicians at the 29th Annual Session in San Francisco, April 19, 1948.

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I. Summary of the General-Adaptation-Syndrome Concept

The pertinent observations made up to the present time are most readily compatible with the following interpretation:

Under the influence of systemic stress, occasioned by a variety of nonspecific damaging agents, the organism responds with a *general-adaptation-syndrome* whose manifestations are essentially independent of the specific nature of the stress employed and depend mainly upon the degree and duration of the exposure. The syndrome evolves in three distinct stages: (1) the *alarm reaction,* (2) the *stage of resistance* and (3) the *stage of exhaustion.* Since hypertension is essentially a disease of the stage of resistance, it will not be necessary to insist upon the other two phases here.

It is thought that at least certain types of spontaneous hypertension in man are due to excessive exposure to *stress* or to derangements in the normal defense reaction against stress. A variety of stresses elicit metabolic changes—the so-called "catabolic impulse" (see below)—which are particularly prominent during the "shock phase" of the alarm reaction, but many of them remain detectable throughout the entire general-adaptation-syndrome.

Apparently this "catabolic impulse" in its turn influences the *anterior-lobe* to produce an excessive amount of corticotrophin. Corticotrophin causes increased corticoid production by the *adrenal.* The corticoids produce involution of the *thymus and lymph nodes* as well as certain *metabolic changes,* for instance: retention of sodium, gluconeogenesis from protein and production by the liver of α_2-globulin (that is, hypertensinogen). Directly or indirectly through their metabolic action, the corticoids also cause a *renal-type of hypertension* with nephrosclerosis. It has not yet been clearly established whether corticoids act first on the kidney and, through the renal-pressor mechanism, secondarily cause hypertension or whether they primarily raise the blood pressure and produce nephrosclerosis as a result of the hypertension. These interrelations are summarized in the graph which also comprises some additional data to be discussed below.

Obviously during stress *sympathetic* stimulation, liberation of *adrenalin* and perhaps even a discharge of pituitary *vasopressin* may likewise contribute to raise the blood pressure, but these effects are rather evanescent and will not be discussed today. They are of importance mainly during acute stresses of short duration.

II. Observations Upon Which the Above Concept Is Based

Let us now discuss the most important observations which led to the formulation of the above concept.

Stress. It was found that many otherwise entirely dissimilar nonspecific damaging agents produce a "catabolic impulse" mainly characterized

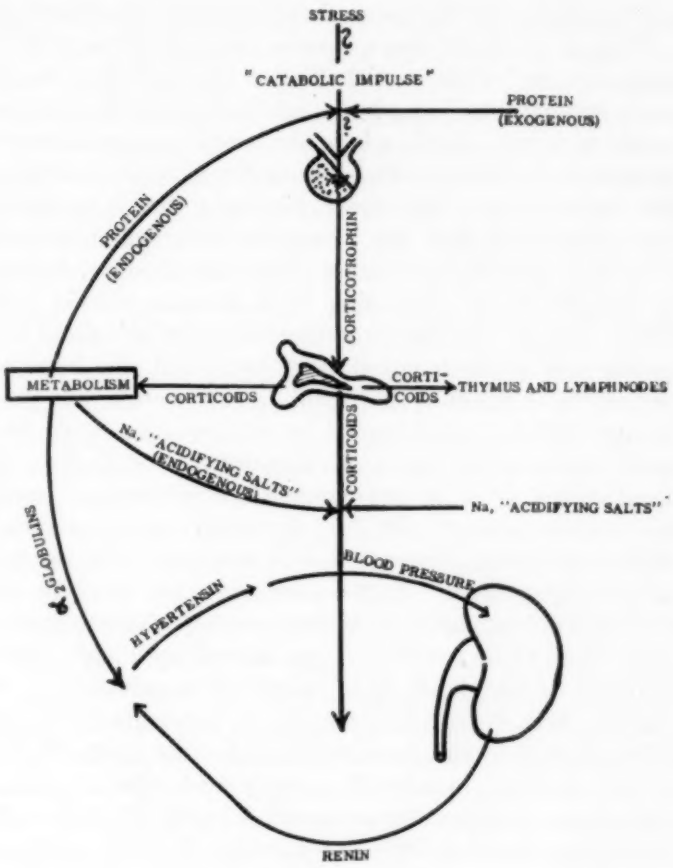

FIG. 1.

by a breakdown of body proteins and an increase in the concentration of protein catabolites and proteolytic enzymes in the blood. This is accompanied by loss of weight and by histologic evidence of a generalized breakdown of cells. At the same time stress elicits a typical alarm reaction with the characteristic adrenal-cortical enlargement, gastrointestinal ulcers, involution of lymphatic organs, etc. Prolonged stress causes less marked catabolic reactions but concomitantly with the adrenal cortical enlargement it can produce nephrosclerosis and hypertension, especially in animals sensitized by unilateral nephrectomy and high-sodium, high-protein diets. The adrenal enlargement is manifestly due to increased corticotrophin production, but it is not quite clear through what pathways stress acts upon the anterior-lobe.

Sayers and Sayers (1947) believe that stress increases the consumption or utilization of corticoid hormones by tissues and that the resulting decrease in their blood-level causes a discharge of corticotrophin by the pituitary

and is thus responsible for the cortical enlargement characteristic of stress reactions. There is no doubt that excessive amounts of corticoids can cause "compensatory atrophy" while partial ablation of the adrenal cortex produces "compensatory hypertrophy" of adrenal cortical tissue because an excess of corticoids tends to depress, while a lack of cortical hormones increases, corticotrophin production by the anterior-lobe under near-physiologic conditions.

Our observations lead us to believe, however, that it is precisely during times of excessive stress that this hormonal self-regulation breaks down. Manifestly the large amounts of urinary corticoids observed during the alarm reaction in human beings (Venning and Browne, 1945; Venning and Kazmin, 1946) indicate that far from there being a lack there is actually an excessive production of corticoids during stress and this hypercorticoidism is sufficiently severe to result in the "spill" of active corticoids into the urine.

Experiments which we performed in collaboration with Misses Stone and Martin showed that the stress of exposure to cold leads to enlargement of the adrenal cortex even in rats which were so severely overdosed with desoxycorticosterone acetate (DCA) that they were anesthetized by it throughout the experiment (intraperitoneal administration of up to 12 mg./100 gm. body weight/day). At the same time the adrenals of these rats discharged their lipid granules in a manner very characteristic of corticotrophin action (judged by frozen sections stained with sudan III and by the brown appearance of the glands upon naked-eye inspection).

Subsequently Mr. Moya of our Institute determined the ascorbic-acid content of the adrenals in rats exposed to cold while under DCA anesthesia. Here again the depletion in adrenal ascorbic-acid, characteristic of corticotrophin action, was demonstrable irrespective of the DCA overdosage. Indeed the damaging effect of DCA intoxication in itself (without exposure to cold) sufficed to cause rapid loss of adrenal ascorbic-acid when the resulting anesthesia was sufficiently profound. Perhaps the reason why Sayers and Sayers (1947) were able to inhibit the loss of adrenal ascorbic-acid by DCA and other corticoids is that they used lesser degrees of stress; as we have said above at near-physiologic levels corticotrophin production is undoubtedly dependent upon the corticoid concentration in the blood.

There are many similar hormonal homeostatic mechanisms which illustrate that the maintenance of important physiologic functions is assured by several alternative regulators. Thus at near-physiologic dose levels, a discharge of insulin tends to decrease the fasting blood sugar but this is counteracted by adrenaline secretion. Indeed there is a direct proportionality between the amounts of insulin and adrenaline which must be simultaneously supplied to assure the maintenance of the glycemic level in the presence of an excess of one of these hormones. However, if excessive doses of insulin are administered, no dose of adrenaline can prevent hypoglycemia. There is no reason to believe that stress actually causes "consumption" of corticoids, but it certainly raises corticoid requirements and thus results in a "relative cortical insufficiency."

At near-physiologic dose levels corticotrophin production—and the resulting adrenal cortical enlargement and activity—depend upon the degree of stress and can be inhibited by exogenous corticoids. Within these limits, the dose of corticoids required to accomplish this is proportionate to the degree of stress. In the event of excessive stress, however, this mechanism becomes comparatively unimportant and other (hitherto not clarified) mechanisms are called upon to augment corticotrophin activity.

The "Catabolic Impulse." As previously stated, stress elicits a catabolic impulse. This is characterized grossly by loss of weight, histologically by death of cells in various organs and biochemically by an increase in the blood concentration of proteolytic enzymes (e.g., fibrinolysin) and protein breakdown products (amino-acids, polypeptides, peptones, uric acid and other N.P.N. constituents). The concomitant hyperkalemia is presumably also due to tissue breakdown. At the same time there may be a rise in the blood concentration of histamine or "H-substance"-like compounds, hypochloremia, hypothermia, a decrease in blood pressure and multiple gastrointestinal ulcers with hemorrhages into the intestinal tract. All these manifestations are especially prominent during the early "shock-phase" of the alarm reaction but may remain manifest to some extent throughout the entire general-adaptation-syndrome. They are not mediated through pituitary, adrenal or renal hormones since none of these manifestations are prevented by hypophysectomy, adrenalectomy or nephrectomy; indeed most of these changes are even more pronounced in hypophysectomized, adrenalectomized or nephrectomized animals because in them stress-resistance is diminished. It is not yet known through what mechanism stress affects corticotrophin production, but the facts established up to the present time are compatible with the view that any, or all, of the catabolic blood-chemical changes may increase corticotrophin production during stress. We know that the nervous stimuli which reach the pituitary directly from the hypothalamus are not indispensable since stress causes adrenal cortical enlargement even after section of the pituitary stalk; it is not impossible, however, that other (e.g., periarterial) nervous pathways may act directly upon the pituitary, and it is certain that nervous (and even purely emotional) stress can cause adrenal cortical enlargement and typical alarm-reaction changes as shown by animal experiments. Perhaps here the nervous stimuli increase corticotrophin production through the intermediary of some blood borne metabolites.

The Hypophysis. Hypophysectomy prevents the production of nephrosclerosis and hypertension by stress, and in the absence of the pituitary more than the mere maintenance dose of hypophyseal extract is necessary to withstand stress. This implies that increased hypophyseal activity (presumably corticotrophin secretion) is essential for resistance to stress and that conversely if such an increased pituitary hormone production is prevented by hypophysectomy, stress no longer affects the adrenal, kidney, blood pressure and the thymico-lymphatic apparatus, hence these appear to be lower links in the chain-of-events than the hypophysis.

Hypophyseal extracts rich in corticotrophin cause adrenal cortical enlargement, nephrosclerosis, hypertension and thymico-lymphatic involution in intact animals but exert none of these effects after adrenalectomy. Hence, presumably the pituitary hormones influence these targets through the intermediary of the adrenal cortex and natural (endogenous) corticoids can produce renal lesions and hypertension.

The Adrenals. As previously stated *adrenalectomy* prevents the involution of the thymus and lymphatic organs which is normally produced either by stress or by anterior-lobe extracts. It also prevents the production of hypertension and nephrosclerosis by anterior-lobe extracts, but technical difficulties make it impossible to establish whether stress could produce these latter changes in adrenalectomized animals since following ablation of the supra-renal stress-resistance becomes too poor to withstand pertinent experiments. Significantly, more than the maintenance dose of corticoids must be administered to adrenalectomized animals if they are to withstand stress. Hence, presumably increased cortical function is an essential part of the defense reaction against stress.

High doses of *mineralo-corticoids,* such as DCA, produce hypertension, nephrosclerosis and involution of the thymico-lymphatic apparatus, irrespective of whether the pituitary or the adrenals have been removed or not. Presumably excessive amounts of corticoids, such as are produced during the general-adaptation-syndrome, can elicit nephrosclerosis and hypertension.

Thymus and Lymphatic Organs. As previously stated, the characteristic involution of the thymico-lymphatic apparatus, seen during the general-adaptation-syndrome, is elicited by a variety of *stresses,* but only in the presence of both anterior-lobe and adrenals. *Hypophyseal extracts* can cause such involution even in hypophysectomized animals (and in the absence of stress), but only in the presence of the adrenals; *corticoids* act in this manner in either hypophysectomized or adrenalectomized animals (and in the absence of stress).

Only direct application of radium or *roentgen-rays* to the thymus region or injection with *folliculoids* and *mustards* has been shown to cause thymico-lymphatic involution in adrenalectomized animals. Presumably these agents have a direct effect upon the lymphatic elements, while all other types of stress, so far examined, act through the anterior-lobe—adrenal-cortex mechanism. It has been claimed that γ-globulins, liberated from the bodies of thymocytes, play an important rôle in serologic defense reactions during stress, but this has not been unanimously confirmed.

The Kidney. The rôle of the kidney in hypertension has been discussed by various authors (see reviews cited in introduction). Suffice it here to examine its participation in the hypertension resulting from exposure to stress.

Manifestly, the hypotension characteristic of the "shock-phase" may so decrease the blood pressure, and hence the blood supply of the kidneys, that renin production is increased as it is after the Goldblatt clamp. Our

experiments have shown, furthermore, that the nephrosclerosis induced by DCA causes hyalinization of individual glomeruli and thus diminishes their blood supply at the time hypertension develops as a result of corticoid overdosage.

Recent experiments with the *"endocrine kidney"* are also relevant (Selye and Stone, 1946). The "endocrine kidney" is prepared by decreasing the renal blood pressure to the level of the colloid-osmotic pressure of blood; under these conditions filtration and urine production cease, while the renal tissue remains sufficiently well supplied with blood to live and to produce hypertensive substances. As far as urine production is concerned, the bearer of an endocrine kidney is exactly equivalent to a unilaterally nephrectomized animal, but unlike the latter it develops marked hypertension and nephrosclerosis in the contralateral, though never in the purely "endocrine," kidney. It appears possible therefore that under the influence of DCA certain individual nephrons, whose glomeruli are severely hyalinized, become transformed into individual *"endocrine-nephrons."* In these transformed units pressor substance production is apparently increased in essentially the same manner as after the "endocrine kidney" operation and hypertension ensues.

Perhaps stress acts upon the blood pressure by increasing first corticotrophin, then corticoid hormone production and through the latter the elaboration of vasopressor substance in individual "endocrine-nephrons."

It may incidentally be mentioned that with the endocrine kidney technic it was possible to demonstrate the following facts:

1. Urine secretion is not essential for the maintenance and endocrine function of renal parenchyma.

2. The renotrophic action of certain steroids (e.g., testosterone) is independent of urine secretion, since it is manifest in the "endocrine kidney." It cannot therefore be regarded as a "work hypertrophy" secondary to metabolic processes which necessitate the formation of urine with special characteristics.

3. The "juxtaglomerular apparatus" is not essential for the production of renal hypertension since in the endocrine kidneys of many animals this region completely disappeared (together with most of the glomeruli), yet the blood pressure rose.

4. Irrespective of urine formation the endocrine activity of the kidney suffices to produce lesions similar to those elicited with DCA.

5. Unlike the cardiovascular damage caused by stress, anterior-pituitary preparations or DCA, that elicited by the "endocrine kidney" is uninfluenced by dietary sodium or protein.

6. Recent experiments which we performed in collaboration with Dr. C. Schaffenburg revealed that rats bearing an "endocrine kidney" develop hypochloremia similar to that caused by DCA, but without any accompanying hypokalemia. This gives further support to our previously expressed

view that the hypokalemia of DCA overdosage is not an important etiologic factor in the production of nephrosclerosis and hypertension by this hormone.

7. Careful histologic study of the endocrine kidney showed that active proliferation with the appearance of numerous mitoses, enlarged cells with polymorph atypical nuclei, loss of eosinophile granules and loss of the brush border, occur especially in the inner zone of the medulla, that is to say where the renal tissue consists mainly of the distal portions of the proximal convoluted tubules. It is rather surprising that a decrease in the blood supply to the renal parenchyma should cause such marked proliferative changes in one specific region while all other parts of the kidney undergo involution and atrophy. Naturally the possibility comes to mind that this zone may be the source of the renal pressor-substances, but at the moment such an interpretation is difficult to prove with certainty.

Trueta (1947) has clearly demonstrated that a decrease in blood pressure—while diminishing blood flow through the renal cortex—augments the circulation through the juxtamedullary zone of the kidney; since it is precisely here that proliferative processes are seen in the endocrine kidney, the question arises whether this growth stimulus could not result from an increased blood supply to this particular zone.

The fact that mitotic proliferation, loss of eosinophile granules, loss of the brush border and proliferation into the lumen with a massive transformation of proximal tubules into solid cords may be the morphologic substrate of renal pressor material, is further supported by an examination of numerous kidneys from patients who died of malignant hypertension and in whom I have seen similar changes although limited to a certain number of nephrons only.

It is not possible with the endocrine kidney technic to answer the important question whether hypertension or nephrosclerosis is the first event to initiate the well known "vicious circle" which develops in animals in which chronic renal hypertension has been produced by various means. In our experiments nephrosclerosis in the contralateral kidney and the rise in arterial pressure developed almost simultaneously. It is for this reason that in the above schematic drawing we do not indicate clearly how the corticoids affect the renal pressor mechanism.

Our experiments do not show that the nephrosclerosis seen during the general-adaptation-syndrome produces hypertension through the renin-hypertension mechanism; it is equally possible that pressor amines or other pressor renal substances are involved. We feel, however, that the bulk of evidence presented by other laboratories is in favor of the renin theory.

III. Factors Influencing the Hormonal Defense Mechanism

Kind of Stress. Earlier work showed that almost any type of systemic damage or stress causes essentially the same alarm-reaction symptoms. It is noteworthy, however, that upon prolonged exposure to stress,

diseases of adaptation (e.g., hypertension and nephrosclerosis) are not invariably produced. In our experiments, exposure to cold proved to be especially conducive to nephrosclerosis, while forced muscular exercise, subcutaneous injection of formaldehyde and other types of stress were less effective in this respect. This is in agreement with the clinical observation that not any type of chronic stress and strain will necessarily lead to nephrosclerosis and hypertension. Indeed, most chronic diseases (e.g., tuberculosis, syphilis, malnutrition) do not have such an effect. Yet, if the mechanism through which stress produces nephrosclerosis and hypertension is the liberation of mineralo-corticoids, it is difficult, at first sight, to understand why the results of stress are not invariably the same. The excess production of corticoids is a non-specific effect of stress, but perhaps the "catabolic impulse" is more dependent upon the specific nature of the damaging agents and intermediate metabolism plays a most important rôle in determining whether the excess mineralo-corticoid material produced results in nephrosclerosis and hypertension.

As we shall see below, even the high doses of anterior-pituitary extracts or DCA are not, in themselves, conducive to nephrosclerosis and hypertension, except after special sensitization (e.g., by diet rich in sodium and protein, partial nephrectomy). Perhaps the specific metabolic effects of stress may similarly sensitize or desensitize the organism to excess mineralocorticoids owing to changes in intermediate metabolism which imitate the derangements produced by the sensitizing or desensitizing diets.

It has been shown that the kidney-damaging action of nephrotoxic sera is increased by simultaneous administration of DCA (Knowlton et al., 1946), and the possibility should be kept in mind that damaging agents produce the changes characteristic of the various "diseases of adaptation" through a dual mechanism; one factor is non-specific (independent of the type of agent and merely dependent upon the degree of damage)—this would be the excess production of corticoids; the other factor is largely specific, and it determines why certain infections, allergies, intoxications and other types of exposure exert a preferential, selective action upon the kidney, the joints, the cardiovascular system, etc.

Diet. Our earlier experiments concerning the sensitization of experimental animals to the nephrosclerosis-producing effect of stress, hypophyseal extracts and DCA have since received ample confirmation. It is now clear that excess sodium, and not chloride, is responsible for this effect of NaCl, since numerous other salts of Na exert a similar effect, while other chlorides are ineffective. It may be added that it is not merely the basic nature of the Na that counts since the salts of other strong bases (e.g., KCl, NH_4Cl) are ineffective. Indeed, excess administration of ammonium chloride, ammonium nitrate, calcium chloride and other "acidifying salts" counteracts the sensitizing effects of sodium and inhibits the production of nephrosclerosis by stress, hypophyseal extracts or DCA.

Recent experiments performed in collaboration with Drs. Hay and Prado showed, furthermore, that protein-rich diets sensitize the organism to the adrenal-cortex-enlarging effect of stress and to the nephrosclerosis-producing and hypertensive actions of anterior-lobe extracts. Curiously, protein-rich diets have no significant effect upon the production of nephrosclerosis and hypertension with pure corticotrophin, DCA or the "endocrine kidney."

More recently we tried to analyze the mechanism through which high-protein diets exert this effect. It was shown that while on synthetic diets containing 30 per cent casein, lyophilized anterior-pituitary material (LAP) regularly causes nephrosclerosis in rats sensitized by unilateral nephrectomy and a high sodium intake, no nephrosclerosis or hypertension occurs if 15 per cent of the dietary protein is substituted by starch.

It is actually the decrease in protein and not the increase in starch that counts, since if the excess starch in a 15 per cent casein diet is substituted by a calorically equivalent amount of fat, nephrosclerosis and the other manifestations of hypertensive disease still fail to occur.

Various protein preparations differ in their ability to cause kidney damage; casein, egg albumin and wheat gluten are more damaging for instance than lactalbumin, gelatin or zein. It would be important to determine whether the effect of certain proteins is due to their content in specific amino-acids or poly-peptides, but among the many amino-acids and amino-acid mixtures which we have examined, none equalled casein in its ability to increase sensitivity to the toxic effects of LAP. However, protein-hydrolyzates and amino-acid mixtures were also effective.

Since protein-rich diets do not significantly augment the nephrosclerotic effect of pure corticotrophin or DCA, it is probable that most, if not all, their effects are due to an increase in the ability of the organism to produce corticotrophin when the requirements for this hormone are high (e.g., stress or LAP). Perhaps this modification of the cortical response is not merely quantitative but even qualitative, inasmuch as protein-rich diets may especially stimulate the production of those corticoids which are particularly active in producing nephrosclerosis and hypertension.

An unpublished experiment of my colleague Dr. Prado is noteworthy in this connection. He found that following unilateral adrenalectomy the compensatory hypertrophy of the remaining adrenal is augmented by high-protein diets, in the same manner as the corticotrophic effect of stress (e.g., cold). It is not yet entirely clear whether the protein-rich diets synergize the action of corticotrophin or whether they increase the endogenous production of the latter when an animal is exposed to stress. This question can only be solved by experiments on hypophysectomized animals injected with a given quantity of corticotrophin, and such experiments are now under way in our Institute. In any case, high protein diets in themselves do not significantly stimulate the adrenal-cortex. Their action becomes manifest only under stress or after partial adrenalectomy, that is at times when corticotrophin production is above normal. This may clarify certain apparent

contradictions in the literature on the effect of dietary protein upon adrenal structure. Perhaps if the diet is in itself damaging and thus increases corticotrophin production, then a high protein concentration is conducive to an excessive cortical stimulation, but such is not the case if the animals are in perfect condition.

Our preliminary observations suggest that perhaps, under the influence of systemic stress, some inactive precursor or activator (enzyme?) normally present in anterior-lobe cells is brought in contact with protein catabolites (substrate?) and that active corticotrophin results from this interaction.

The following simplified table may help to summarize our observations concerning the principal factors influencing the hormonal production of nephrosclerosis and hypertension.

TABLE I

Factors Influencing the Production of Nephrosclerosis and Hypertension by Stress, Hypophyseal Extract (LAP), Desoxycorticosterone Acetate (DCA) or the "Endocrine Kidney" (↑ = increase; ↓ = decrease; + = action present; 0 = no action; ? = pertinent experiments suggestive, but, due to high mortality inconclusive)

Hypertensive agent	Na ↑	NH_4Cl ↓	Adrenal-ectomy ↓	Hypophys-ectomy ↓	Protein
Stress	+	+	+(?)	+(?)	+
LAP	+	+	+	0(?)	+
DCA	+	+	0	0	0
Endocrine kidney	0	0	0(?)	0(?)	0

IV. Clinical Implications

Several recent publications indicate that the diseases of adaptation develop in man essentially in the same manner as in experimental animals. It is particularly noteworthy that increased corticoid elimination in the urine has been demonstrated by actual bioassay (Venning and Browne, 1945; Venning and Kazmin, 1946); that the adrenal-cortex of man increases in width and activity (as judged by histologic studies) following exposure to non-specific damage (Zamchek, unpublished); and that renin is present in comparatively high quantities in the blood of the renal vein in man (Haynes et al., 1947). It is true that in hypertensive patients the renin concentration of the kidney vein was not significantly higher than in intact controls, but the procedure (catheterization of the kidney vein) is in itself a damaging agent, and hence the controls can hardly be considered as having been examined under true basal conditions.

It is also significant that in certain types (especially in the malignant types) of nephrosclerosis and hypertension where there is hypochloremia, alkalosis and low sodium diets or treatment with ammonium chloride sometimes prove highly effective in depressing the blood pressure (Viersma, 1946; Selye, 1946), and that diets consisting mainly of rice and fruit juices (Kempner, 1945) likewise tend to depress the blood pressure in hypertensive patients. In the light of the above experimental investigations it is highly

improbable that these rice and fruit juice diets act by virtue of some hypothetic, specific depressor substance contained in them; such food is extremely poor both in sodium and in protein which, in itself, could explain its beneficial action.

Summary and Conclusions

The principal observations upon which the concept of the "General-Adaptation-Syndrome" and the "Diseases of Adaptation" is based have been reviewed with references to the main pertinent literature. Special emphasis has been placed upon certain recent observations indicating that a number of metabolic factors can modify the pathogenicity of mineralo-corticoids produced in response to stress. Thus diets poor in sodium and protein as well as treatment with acidifying salts (e.g., NH_4Cl, $CaCl_2$) tend to prevent the development of nephrosclerosis and hypertension under various experimental conditions.

Clinical observations indicate that in man the diseases of adaptation develop essentially in the same manner as in experimental animals and are accompanied by similar hormonal derangements. In certain cases low-protein diets or treatment with ammonium chloride proved beneficial, but this was not invariably the case, and much further work will be required before the results of the above experimental investigations can be fully utilized in clinical medicine.

Acknowledgments

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SERIAL ELECTROCARDIOGRAPHIC CHANGES IN YOUNG ADULTS WITH ACUTE RHEUMATIC FEVER; REPORT OF 62 CASES *

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INTRODUCTION

Purpose and Material

ALTHOUGH no electrocardiographic pattern is specific or diagnostic of acute rheumatic carditis, it is well known that changes do occur which can be correlated with the clinical findings of this disease. Abnormalities of the electrocardiogram which are often seen in acute rheumatic fever have also been recorded in other diseases such as pneumonia, diphtheria, influenza, brucellosis, and typhoid. The value of the electrocardiogram in the diagnosis of myocarditis is well established.[1]

It is generally accepted that increase in the PR interval frequently occurs in acute rheumatic carditis. Less well-known abnormalities of the electrocardiogram have been reported, such as elevation or depression of the R-T or S-T segments,[2, 3, 4] S_{-1}, Q_{-3} and Q_{-1}, S_{-3} patterns,[5] prolongation of the duration of electrical systole (Q-T interval),[6] low voltage T-waves,[7] straightening of the ST or RT border,[4, 8] and the occurrence of "the coronary T-wave." [9]

It is the purpose of this article to present the electrocardiographic changes found during the course of the initial attack of proved rheumatic fever in a group of 62 young, white males. This group was made up of soldiers ranging in age from 17 to 21 who entered the Fort George Wright Regional and Station Hospital between January 1, 1946 and April 25, 1947. Each of these cases was under our personal clinical observation.

In no instance was there a previous history of rheumatic fever or chorea per se. Ten members of our group, however, had a history of fleeting joint pains or epistaxis or both at some time during their childhood.

In every instance the chief complaint was subacute or acute arthritis involving one or more joints of the four extremities. On entry these patients had a fever ranging between 99.8° F. and 105° F. orally. A leukocytosis ranging from 11,000 to 20,000 was found in each case on the day of entry. In all but one case there was an elevation of the sedimentation rate above 25 mm. per hour (Westergren method) during the period of hospitalization.

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A mitral systolic murmur of varying intensity was found in 80 per cent of the cases on the first day of entry. Pleuritic chest pain associated with crepitant râles was found in 32 per cent of the cases. A tachycardia was present in 90 per cent of our cases on the day of entry.

In all members of this group, initial treatment consisted of bed rest and 5 to 15 grams of sodium salicylate, orally administered daily in divided doses. Supportive treatment consisted of vitamin supplements in addition to a high caloric diet as tolerated and the cautious administration of parenteral fluids in a few cases evidencing dehydration on entry. Electrocardiograms were obtained every other day during the first week of hospitalization and twice a week thereafter. These patients were followed for a period of six weeks and then were transferred to a General Hospital for convalescence of varying periods. It should be emphasized that in the present study we are concerned only with the initial attack of acute rheumatic carditis and not with the problems of the disease process as presented by chronic rheumatic heart disease.

Our methods of measuring our electrocardiograms and our criteria for abnormality are given as follows: We routinely obtained two Lead III's in each case; Lead IIIa was taken with normal respiration and Lead IIIb was taken during held inspiration. The PR intervals were measured in Lead II routinely and the duration of the QT intervals was taken as the longest QT interval in any of the limb leads. The QT interval was considered prolonged when K in the formula $QT = K \sqrt{\text{cycle}}$ exceeded 0.40 second. The precordial lead was taken routinely at CF4, but it was not thought to be constant enough for technical reasons to be taken as an accurate measurement for the purposes of this study. All changes reported in our table of abnormalities occurred in the limb leads. In all instances, unless specifically qualified, our criteria were based upon those given by the New York Heart Association and adopted and distributed by the American Heart Association.[10] Left deviation of the electrical axis was considered present only when the algebraic sum of the QRS deflections was positive in Lead I and negative in Lead IIIb (taken during held inspiration). Similarly, right deviation of the electrical axis was considered present when the algebraic sum of the QRS deflections was negative in Lead I and positive in Lead IIIb. A tendency towards right deviation of the electrical axis was reported when QRS deflections in Lead I equalled zero and were positive in Lead IIIb.

Case Presentations

We have selected six cases which we believe to be representative of our group and which gave evidence of electrocardiographic changes that we considered to be abnormal and of particular interest.

Case 1. A 21 year old white male entered the hospital with a chief complaint of polyarthritis and pleuritic-like chest pains of three days' duration. A diagnosis of acute rheumatic fever was made on the basis of acute polyarthritis, fever, leukocyto-

sis and an elevation of the sedimentation rate to 40 mm. per hour. A tachycardia and a transitory mitral systolic murmur were present on entry. Rheumatic pneumonitis was diagnosed clinically, and a patchy infiltration of the pulmonary parenchyma was seen in the roentgenogram of the chest. Serial electrocardiograms revealed a transitory, first degree auricular ventricular block and the development of an S_{-1}, Q_{-3} pattern (figure 1). An S_{-2} over 3 mm. was present. The point of particular interest was the development of the S_{-1}, Q_{-3} pattern. Although a deep S_{-1} was present on the initial record, Q_{-3} did not become pronounced until three days later. At that time it was more than 25 per cent of the largest QRS deflection in any of the limb leads. This pattern developed with a prolonged, severe, rheumatic pneumonitis, a rheumatic carditis, and a mitral systolic murmur.

Case 2. A 17 year old white male entered the hospital with the chief complaint of polyarthritis, pleuritic-like chest pains and marked dyspnea of 24 hours' duration. On entry the patient had rheumatic pneumonitis confirmed by roentgenogram, a gallop rhythm, and a pericardial friction rub. The pericardial rub persisted for 24 hours. A grade II mitral systolic murmur and extension of the area of cardiac dullness 2 cm. to the left of the midclavicular line were found on physical examination. His sedimentation rate was 90 mm. per hour. Associated with the pericarditis, the patient's electrocardiogram revealed the following (figure 2): Elevation of the ST_{-1} and ST_{-2} segments; a prolonged PR interval; T_{-1} less than 1 mm., T_{-2} diphasic and T_{-3} inverted. Of particular interest was the "coronary type T-wave" seen in CF_4, on September 19, 1946 (the "coronary T-wave form" consists of an upward convexity of the ST or RT segment with an inverted T-wave). On September 24, 1946, a "coronary type T-wave" was seen in Lead I as well as Lead IV; T_{-1} was then inverted to diphasic and T_{-4} was sharply inverted; T_{-2} was diphasic and T_{-3} was upright to diphasic, but low. In this tracing, too, it should be noticed that the previously elevated ST segments in Leads I and II returned to the iso-electric line, having borne a time relation to the clinical evidence of pericarditis. On the tracing of October 3, 1946, the "coronary T-wave form" entirely disappeared; T_{-1} was flat; T_{-2} was upright, but low; T_{-3} was flat and T_{-4} was upright. A low R_{-4} was seen in the Lead CF4 on this date. This may have been due to failure in placing the precordial lead in the same position used previously and subsequently. The record of October 31, 1946 showed a return of the pattern toward normal. T_{-1} and T_{-2} were upright and normal, and T_{-3} was upright to flat. Straightening of the ST border was present in this record in Leads I and II. The electrocardiogram on November 4, 1946 was essentially normal although some straightening of the ST_{-1} border was still present. This case represents a severe clinical pericarditis and myocarditis.

Case 3. A 19 year old male entered the hospital with the chief complaint of polyarthritis. On the day of entry he had a leukocytosis, fever and rheumatic pneumonitis. We are mentioning this case because it showed a change from a tendency to right deviation of the electrical axis to unequivocal right axis deviation and because it showed the formation of an S_{-1}, Q_{-3} pattern (figure 3). It should be noted at this point that the Q_{-3} was less than 25 per cent of the height of the QRS segment in any one of the limb leads. We interpret a tendency to right deviation of the electrical axis when the algebraic sum of the QRS deflections in Lead I is zero and Lead III is positive. It will be noticed that this tendency became actual right deviation of the electrical axis in a period of about three weeks.

Case 4. A 17 year old white male entered the hospital with the chief complaint of polyarthritis, chills and fever of 24 hours' duration. On the day of entry the patient had a leukocytosis, fever, and a sedimentation rate which was 119 mm. per hour. A tachycardia was present on entry, but there were no murmurs on auscultation of the heart. Within the 48 hours after entry the patient developed a grade I mitral systolic murmur which persisted until he was transferred to a General Hospital for convalescence. This patient is presented because his electrocardiogram demonstrated

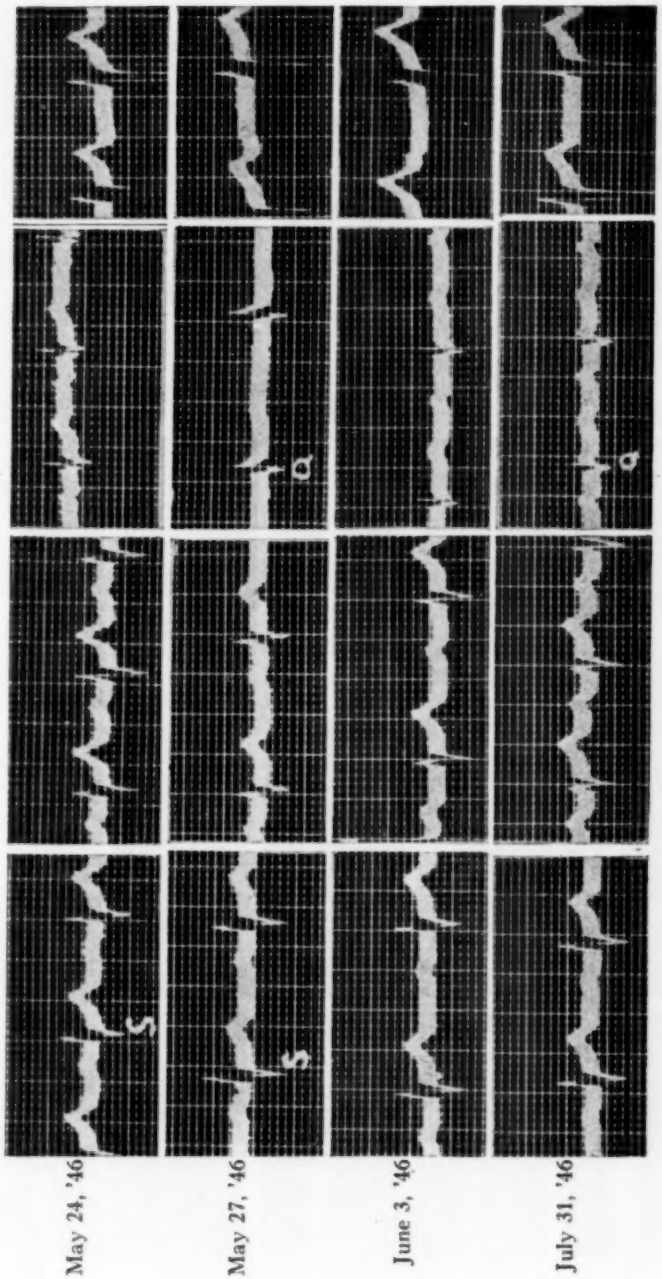

FIG. 1. *Case 1.* Note development and changing relationships of S_{-1} and Q_{-3}.

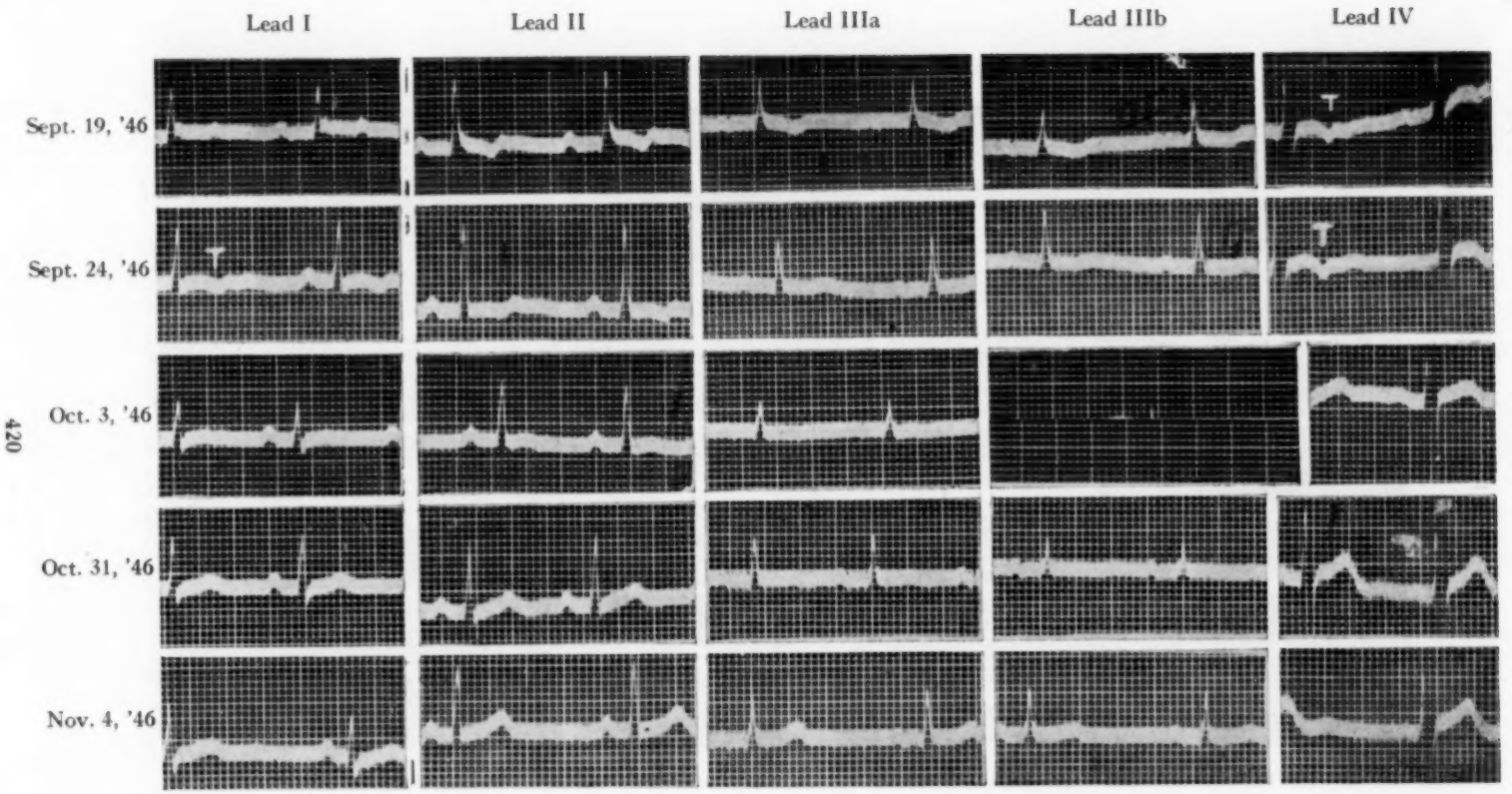

FIG. 2. *Case 2.* Note development of "coronary T-wave" first in Lead IV of September 19, 1946 and then in Lead I and Lead IV of September 24, 1946.

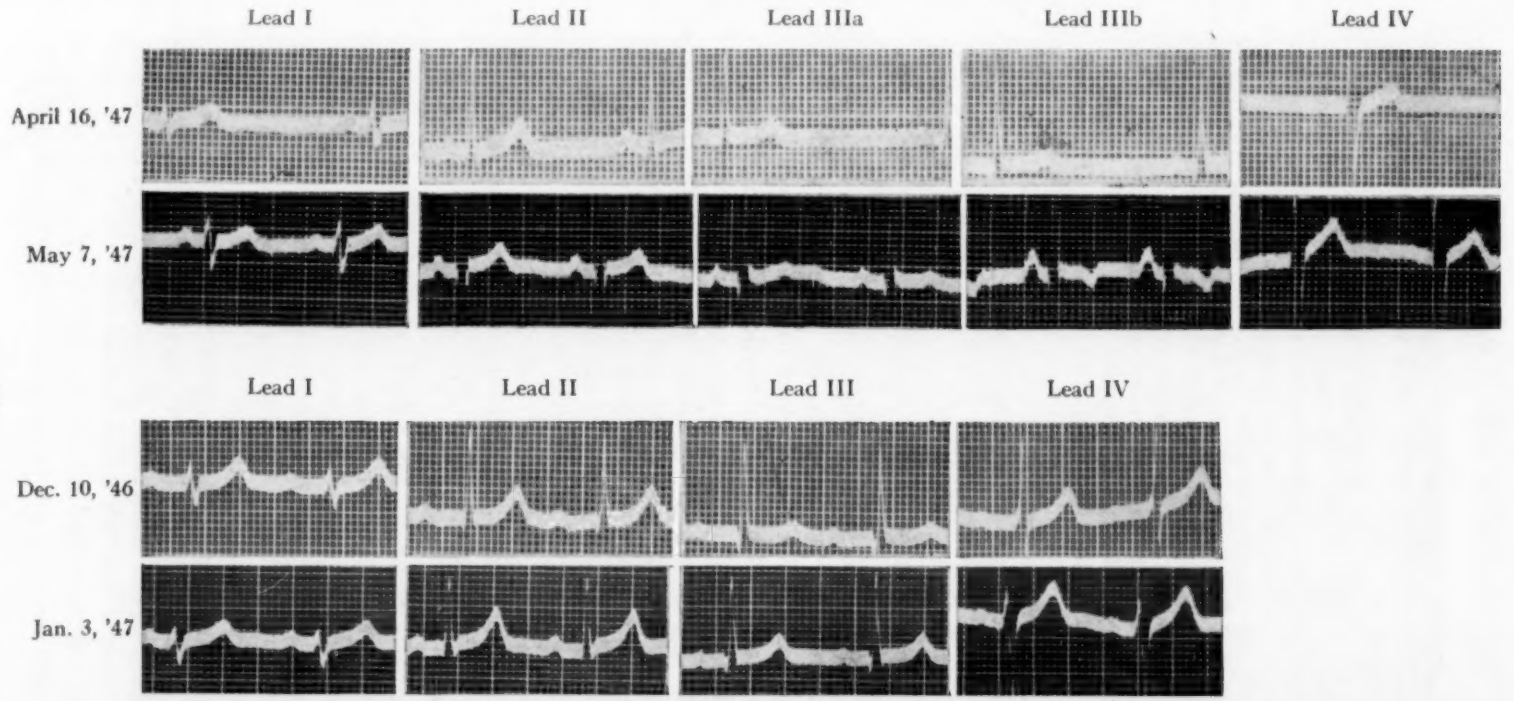

FIG. 3. (above) *Case 3.* Note shift from tendency to right deviation of the electrical axis to right deviation of the axis between April 16, 1947 and May 7, 1947. (below) Clinical course similar to Case 3 above, but not included in statistics of present report. Note shift toward right axis deviation.

a progressive auricular ventricular block (Wenckebach phenomenon). A slight elevation of the ST segments in Leads I and II was noted during the patient's course in the hospital (figure 4).

Case 5. A 17 year old white male entered the hospital with the chief complaint of migratory joint pains of 24 hours' duration. On entry he had acute polyarthritis, pleuritic-like chest pains, fever, sinus tachycardia and a sedimentation rate of 78 mm. per hour. This case is presented because it demonstrated a wandering pace-maker. Forty-eight hours after demonstrating the latter, the electrocardiogram was found to have a PR interval of .28 second. The first degree heart block is not illustrated.

Case 6. A 20 year old soldier entered the hospital with the chief complaint of polyarthritis and palpitation of one week's duration. A diagnosis of acute rheumatic fever was made on the basis of an elevated sedimentation rate which was 50 mm. per hour on entry, leukocytosis, tachycardia, polyarthritis, fever, and a grade I mitral systolic murmur with a changing electrocardiogram. The patient's electrocardiogram has been reproduced to show the prolongation of the duration of electrical systole (QT interval) which was evidenced in Leads I, II, and III, in which K in the formula $QT = K\sqrt{cycle}$ was 0.42 second in the longest QT of the limb leads. Of incidental interest is the deep S_2 which projected downward for a distance of 4 mm. (figure 6).

Discussion

General. The electrocardiographic changes in the acute phase of rheumatic carditis are based on the changing inflammatory state of the tissue reaction of the heart. The pathology of this state is well known to consist of acute inflammation, edema and leukocytic infiltration of the heart tissues. Aschoff's bodies in the interstitial tissue and a rheumatic arteritis are invariably present. It is not strange, therefore, that, with such alterations in the pericardium, myocardium, valves and blood vessels, a corresponding alteration in the physiology and anatomy of the heart takes place.

It was often found in the course of our investigation that a single electrocardiogram was interpreted as normal, but that subsequent records, themselves probably within normal limits, showed peculiar variations from record to record on the same patient. The concept of a changing inflammatory state of the myocardium giving rise to a changing pattern on serial records is vital to the understanding of the electrocardiograms of acute rheumatic carditis. Although any particular record in a patient's series might be interpreted as within normal limits, inspection of the serial records of the patient left no doubt of the abnormality of the series.

In the course of this study, many transient changes were noted in the electrocardiographic patterns. It has been clearly shown that salicylates have no effect whatsoever on the normal electrocardiogram.[11] Extensive studies have shown that salicylates have not been proved to affect in any way even the AV conduction time in acute rheumatic carditis.[12] Therefore, we have concluded that the changes we observed were not due in any part to the salicylate therapy that was given routinely.

Our patients were all bed patients at least for the first three weeks, and the tracings were taken in a recumbent position with a single pillow under the head.

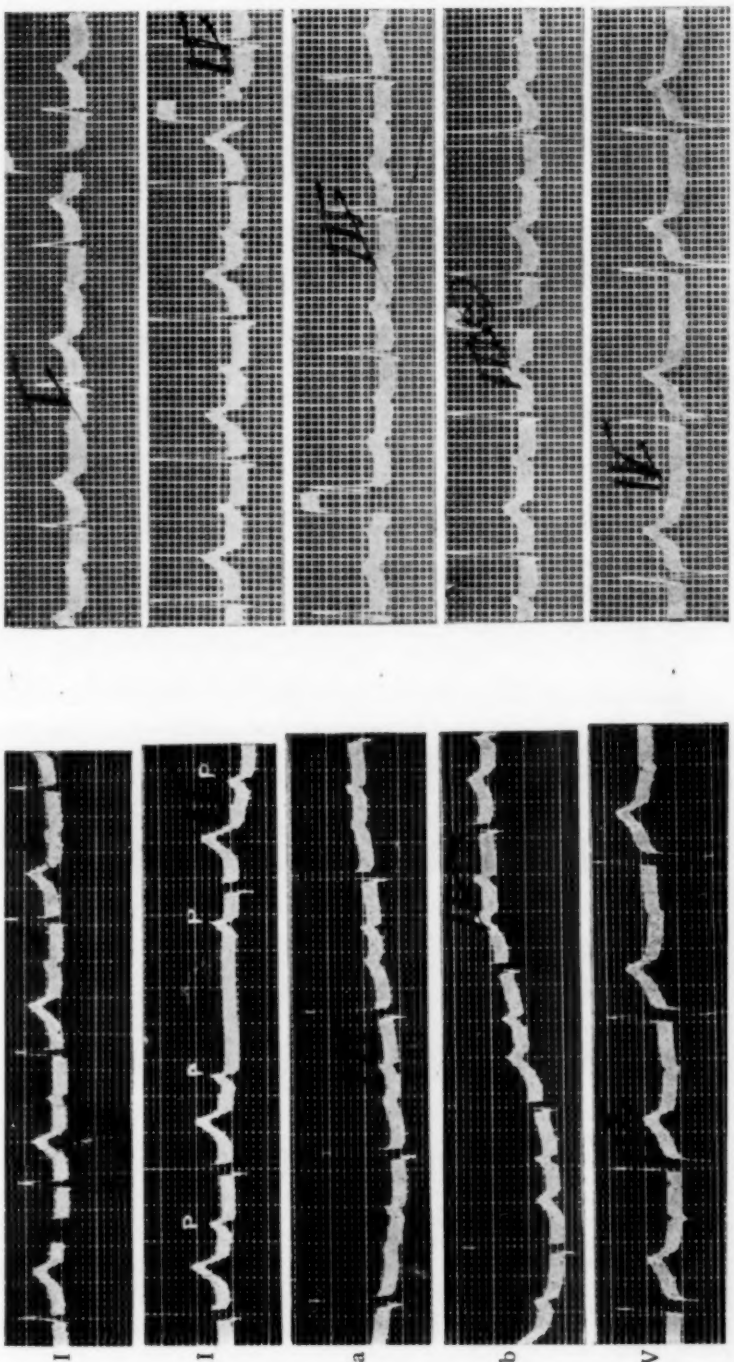

FIG. 4. *Case 4.* Note increasingly prolonged PR interval with eventual dropping of a beat in Lead II of February 26, 1947.

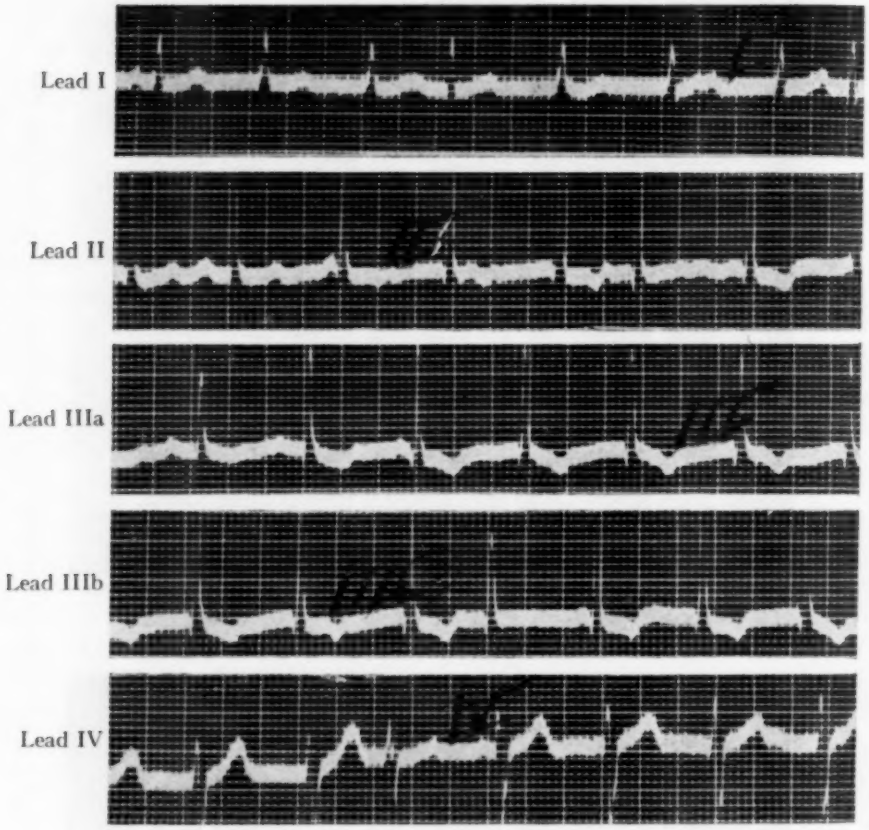

FIG. 5. *Case 5*, demonstrating a wandering pacemaker.

TABLE I

Summary of Electrocardiographic Changes Found

Category	Number of Cases	Per Cent of Total
T-wave alteration including changes in the ST segments	38	61.2
First degree, auricular ventricular block	26	41.9
Prolongation of QT interval	22	35.0
Abnormal fluctuation of the level of the ST segments (elevation and depression)	14	22.5
S_{-1}, Q_{-2} pattern	7	11.2
Inversion of limb lead T-waves	7	11.2
S_{-2} greater than 3 mm. without axis deviation	7	11.2
Q_{-1}, S_{-3} pattern	3	4.8
Transitory AV nodal rhythm	3	4.8
Left axis deviation	2	3.2
Right axis deviation	1	1.6
Right bundle branch block	1	1.6
Wenckebach phenomenon	1	1.6
Normal	1	1.6

61 (98.4 per cent) of the 62 patients had one or more of the electrocardiographic changes listed.

We have utilized the fact that the electrocardiographic pattern in a given normal individual remains uniformly constant from time to time and day to day.[8, 13, 17] Alterations in the pattern do, in fact, occur, but these cannot be recognized in the least as distinct and different from one record to another.

P-R Interval. As was anticipated, a large number of our cases showed transitory prolonged PR intervals (41.9 per cent) (table 1). All of these

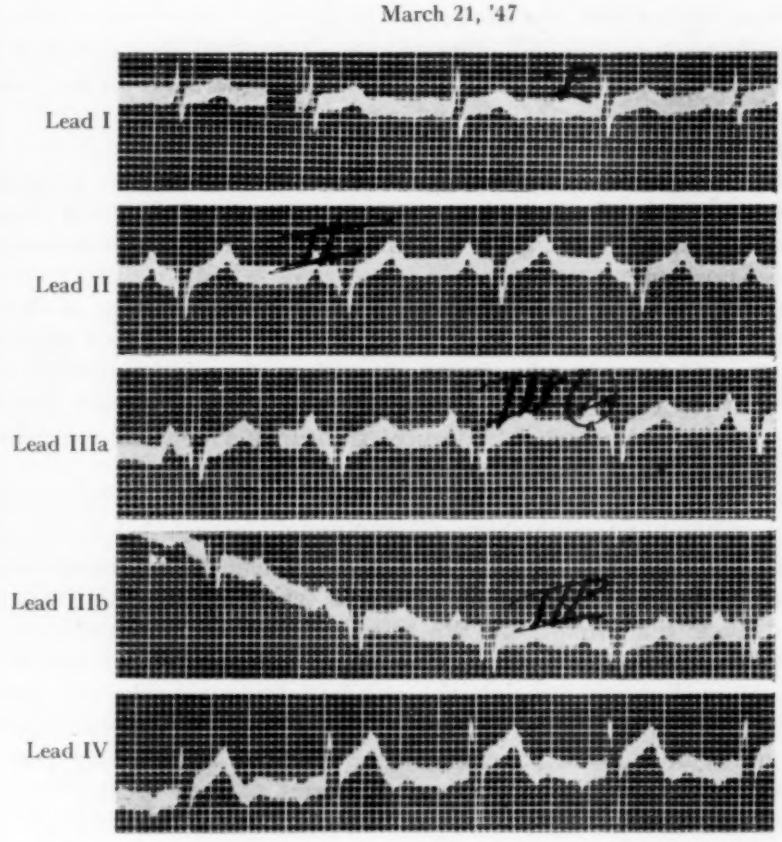

FIG. 6. *Case 6.* Note prolongation of the duration of electrical systole (Q-T interval).

returned to normal before transfer for convalescence. The return of the PR interval to normal has been looked upon with confidence as a sign of cessation of rheumatic activity. However, in three of our cases with apparent clinical remission and the return of the PR interval from abnormal to normal, a subsequent flare-up occurred with the reappearance of the first degree heart block. Subsequently, the PR intervals returned to normal. These findings seem to indicate that our criteria for quiescence of this disease are far from absolute. Convalescence in this disease should probably be longer than has been generally regarded as sufficient.

A transitory Wenckebach phenomenon showing progressive lengthening

of the PR interval with eventual dropping of the beat was seen in one case (see case 4, figure 4).

No cases of complete AV block were recorded.

Q-T Interval. The duration of electrical systole (the Q-T interval) was found to be prolonged in 35 per cent of our cases. A previous study [6, 16] reported that 100 per cent of their cases of acute rheumatic carditis showed prolonged Q-T interval. These cases were primarily children and in a much younger age group than our cases.

The duration of the Q-T interval was determined by calculating K in the formula QT interval $= K \sqrt{\text{cycle}}$. We considered K to be abnormal when it was greater than 0.40 second in any of the limb leads.

Some observers believe that there is little practical value in measuring the duration of electrical systole (Q-T interval).[14] However, we found its determination to be of some value. In four of our cases of clinical rheumatic fever with rheumatic carditis, it was the only demonstrable deviation in the electrocardiogram.

Normals. With serial electrocardiograms taken routinely, as described previously (every other day for the first week and then twice a week thereafter), one (1.6 per cent) of our cases showed entirely normal records throughout the entire period of observation. It is conceivable that if the records had been taken more frequently, transitory abnormalities might have been detected even in this case.

The extent of rheumatic inflammation and its location is probably of some importance as to whether or not changes are recorded in the electrocardiographic tracing. The fact that 98.4 per cent of our patients showed abnormalities in their electrocardiographic series indicates the widespread acute damage that occurred. We assume that the one normal case may have had rheumatic lesions on such a small scale as to be undetectable by the electrocardiogram utilizing the standard leads. Again we emphasize the importance of change in the records. In effect the whole series of electrocardiograms of a given patient is more sensitive in detecting pathologic lesions than any one of the records in the series.

Rhythms. A variety of unusual rhythm such as auricular premature contractions, ventricular premature contractions, nodal rhythms, sinus bradycardia and paroxysmal tachycardia were noted but were not included in the present study as abnormal, for these may occur in normal people. However, in the presence of an irritable, inflamed myocardium, they may be of significance. Two cases of wandering pacemaker were recorded. Auricular fibrillation and auricular flutter were not seen. Ventricular rhythms other than ventricular premature contractions did not occur.

QRS Changes. There were no records of abnormal forms of the component waves of the QRS complex considered by themselves. However, several deviations which have been thought to be due to strain on the right or left heart became apparent. Cross patterns of S_{1-}, Q_{-3} and Q_{-1}, S_{-3} type

were considered present whenever such patterns were found or developed in the course of the disease. We made no attempt to set down criteria for the height of these waves before they should be considered significant. Their mere existence in these combinations has been found to be three times more frequent in children with rheumatic heart disease than in normal children.[5] Although we consider such combinations in themselves suggestive of abnormality, in every case reported with these patterns other evidence of active carditis in the serial electrocardiograms was present.

It may be that such cross patterns represent the early initial phases of the anatomical alteration in the heart which ultimately lead to deviation of the electrical axis, so often seen in rheumatic heart disease. The S_{-1}, Q_{-3} pattern has been thought to represent early right heart strain and the Q_{-1}, S_{-3} pattern early left heart strain. In this connection, Case A with severe rheumatic pneumonitis developed a prominent Q_{-3} in a period of three days to show a definite S_{-1}, Q_{-3} cross pattern. We postulate that this was due to right heart strain from the burden of an inflamed myocardium, mitral valvular disease, pulmonary disease, and increased pulmonary arterial tension secondary to widespread rheumatic arteritis of the pulmonary vessels.

An S_{-1}, Q_{-3} pattern occurred in 11.2 per cent, and a Q_{-1}, S_{-3} pattern in 4.8 per cent of our cases.

A large number of our cases had rheumatic pneumonitis (32 per cent). Our clinical criteria for such a diagnosis were the rheumatic picture plus dyspnea, pleuritic pain on respiration, crepitant râles and roentgen-ray evidence of patchy infiltration in the vast majority of the cases so diagnosed.

When no deviation of the electrical axis was present, 11.2 per cent of our cases showed an S_{-2} which was less than 3 mm. initially and which became greater than 3 mm. during the period of hospitalization. The significance of this finding is not clear, but it did occur in a sizeable percentage of our cases of acute rheumatic carditis. An S_{-2} greater than 3 mm. in the absence of axis deviation may occur normally, but it may also be associated with evidence of organic heart disease.[15]

Surprisingly few cases showed axis deviation. Left deviation of the electrical axis was seen in 3.2 per cent of our group. Frank deviation of the electrical axis to the right was seen in only one case. In general then, it appears that deviation of the electrical axis is primarily a manifestation of prolonged established rheumatic heart disease.

RT or ST Period and T-Wave Changes. "The period from the end of the R-wave or S-wave to the end of the T-wave may be divided into two portions; the first portion terminates at the onset of the T-wave and the second portion is occupied by the T-wave itself. Alterations may be distinguished which involve these segments either separately or together."[8] In the normal electrocardiogram at the conclusion of the R-wave or S-wave, a short iso-electric period (RT or ST segment) occurs during which a slight upward slope may be present. This is followed by a definite change in the direction of the slope of the string to begin the T-wave.

Alterations in the second portion, or T-wave, consist of high voltage T, low voltage T, flat T, inverted T, peaking of T, and asymmetry of T. We took two Lead III's in order to lessen the normal variation that is usually seen in the T-wave of this lead. Lead IIIa was taken as the usual records with normal respiration. Lead IIIb, however, was taken in held inspiration.

Changes in the first portion (RT or ST segment) of the curve were mostly confined to fluctuations in the elevation and depression of these segments as compared to the level of the PR interval as a baseline (figure 7). These changes occurred in 22.5 per cent of our cases. In cases of clinical pericarditis and anoxemia of the heart muscle, changes in the level of the RT

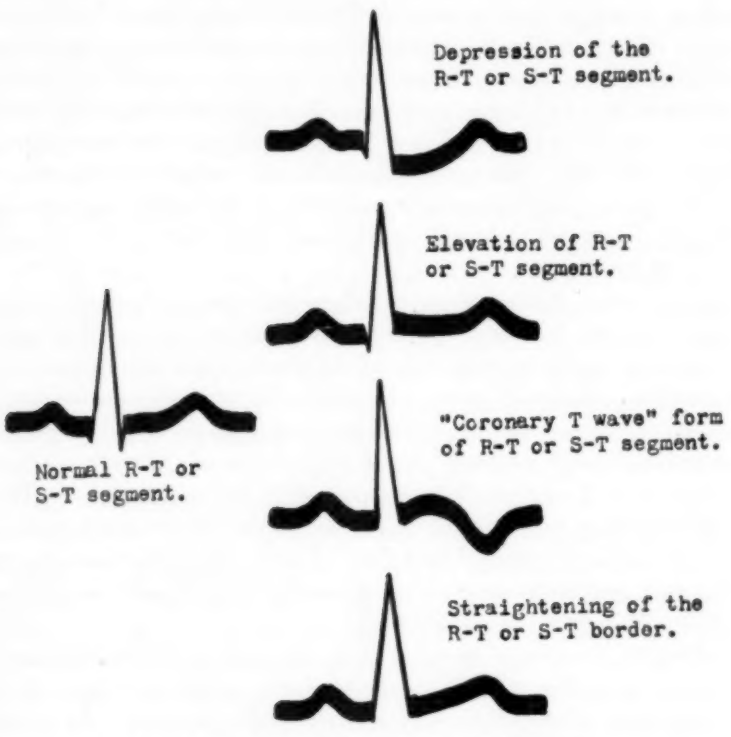

FIG. 7. Abnormalities of the R-T or S-T segment.

or ST segments have been observed. It has been shown repeatedly that unchanging slight elevation or depression of these segments per se are of no great clinical importance. Fixed elevation of this segment is frequently seen in the chronic phase of rheumatic heart disease. This is not found characteristically in acute rheumatic activity and is probably due to myocardial fibrosis secondary to the residual pathologic lesions associated with acute attacks of rheumatic inflammation. Indeed, fixed elevation of this segment has often been seen in perfectly normal individuals.[15, 17] We did not consider any of our cases to have abnormalities of the RT or ST seg-

ment which did not show a continual changing, fluctuating position of the segment, varying between elevation and depression, of 1 mm. or more.

The changes seen as a combination of the RT or ST segments and the T-wave consisted of the occurrence of the "coronary T-wave," and the straightening of the ST or RT border. Both of these abnormalities are shown on the record of case 2 and figure 2 (see also figure 7).

The "coronary T-wave" consists of a downward directed T-wave with an RT or ST interval showing an upward convexity which lies at the zero point of the record or above it.[9] Although this change is often seen in coronary disease, it has also been implicated in rheumatic carditis and may be due to pericarditis with complicating myocarditis.[3, 9]

Straightening of the RT or ST border consists merely of the loss of the change of slope of the line which normally begins at the beginning of the T-wave. This results in a straight sloping line from the end of R or S to the peak of T (figure 7). This occurred in 28 (45 per cent) of our cases and was most frequently found in Leads I and II. High voltage T-waves (greater than 0.5 mv.) were found in 20 cases and were always associated with straightening of the ST border. It will be seen from table 1 that the most frequent changes observed occurred in the T-wave portion of the tracing (61.2 per cent). We found then that the RT or ST period and the T-wave portion of the curve changes more frequently away from the normal in this disease than does the duration of the PR interval (41.9 per cent in our series) which has been thought to be one of the most frequent changes in the electrocardiogram of rheumatic carditis.

General Discussion

It should be noted that in all cases presented the changes are transient and indicate the transitory damaging effect of the acute rheumatic involvement of the heart. This is easily understandable in the light of the well-known transitory manifestations of this disease in the joints, skin, lungs, and other tissues. That permanent damage does occur is beyond dispute, but apparently the amount of tissue attacked in the initial phases is far more extensive than that in which chronic damage remains.

All of the 98.4 per cent of cases showing abnormalities in their serial records showed these changes within the first two weeks of the onset of the clinical symptoms. Therefore, by taking between five and six records during these first two weeks, valuable objective confirmatory evidence of rheumatic carditis was recorded. The routine suggested is an electrocardiogram taken every other day for the first week, and an electrocardiogram twice in the second week. We believe this routine to be both practical and economical in the use of the electrocardiogram as contributory evidence in the diagnosis of suspected clinical rheumatic fever. A high expectation of confirmatory evidence by demonstration of abnormalities described in this paper can be expected.

Summary and Conclusions

The electrocardiographic findings of serial electrocardiograms in 62 cases of the initial attack of proved acute rheumatic fever in young adults are presented. These findings are correlated with the clinical course in six particularly interesting cases.

If records are taken every other day during the first week and twice a week thereafter in cases of acute rheumatic fever, a high percentage of abnormal serial electrocardiograms due to rheumatic carditis will be obtained. This is of considerable value in the differential diagnosis of this disease.

A much larger number of cases showed changes in the RT or ST segment and T-waves (61.2 per cent) than showed prolonged PR intervals (41.9 per cent). This seems to indicate that rheumatic activity, as demonstrated by electrocardiographic changes, more often affects the ventricular myocardium than the A-V conduction tissue alone.

The return of the electrocardiogram to normal cannot be taken as a criterion for complete remission of rheumatic activity.

Although minor variations of the electrocardiographic pattern probably do occur in normal individuals, these are extremely slight and not recognizable as abnormal fluctuations. The most valuable single concept of the electrocardiogram in the diagnosis of rheumatic carditis is that of the changing pattern in serial records corresponding to the changing inflammatory state of the heart, to show abnormal fluctuations during the course of the disease.

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NEURONITIS AND NEURONOPATHY: FURTHER EXPERIENCES WITH TYPHOID VACCINE THERAPY *

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Acute inflammatory disease of the peripheral nerves and nerve roots, alone or in combination with involvement of the brain, brain stem or spinal cord, has been the subject of numerous reports since the original article by Osler [1] in 1892. These isolated, sporadic cases and groups of cases of almost epidemic proportions have been characterized by protean symptoms and findings. Despite numerous efforts at isolation of a definite causative organism, none has been consistently found, and we have had to accept the general impression that a virus is the most likely etiological factor. Mills,[2] in 1898, first suggested the term "neuronitis" for this disease. In 1916, Guillain, Barré and Strohl [3] reported a series of cases, all of whom recovered. They first drew prominent attention to an increase in spinal fluid protein without any increase in cells and suggested the designation "albumino-cytologic dissociation." They indicated that this implied a good prognosis. In subsequent studies, depending upon the symptomatology of the cases reported, the disease has been reported under many descriptive names such as "infectious polyneuritis," "encephalo-myelo-radiculoneuritis," "infective neuronitis," or simply as the "Guillain-Barré syndrome," even in the absence of albumino-cytologic dissociation.

Since the study of Guillain, Barré and Strohl, numerous reports have challenged the concept that an albumino-cytologic dissociation indicated a good prognosis. In 1918, Bradford, Bashford, and Wilson [4] reported a 26.6 per cent mortality in 30 cases. Gilpin, Moersch and Kernohan,[5] in 1936, reported a 14 per cent mortality in 35 cases, and Forster, Brown and Merritt,[6] in 1941, reported a 42 per cent mortality in 26 cases. DeJong,[7] in 1940, presented 15 cases with a 13.3 per cent mortality. He divided his cases into three types, according to end results: (a) those who recovered completely in an average of eight weeks, (b) those with an incomplete recovery and a prolonged course, (c) those with a fatal termination. He concluded that from the type of onset, early clinical course and laboratory findings, one is unable to foretell the outcome. Roseman and Aring [8] reported 16 cases with an 18 per cent mortality. They estimated the duration of an acute phase from two weeks to four months, and a total duration of illness varying from eight weeks to three years. It seems evident, therefore, that even albumino-cytologic dissociation is not reliable in prognosis as to

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life itself. The duration of illness is often prolonged to three years with residual symptoms still present.

In spite of such uncertainty as to prognosis, treatment has been largely supportive in nature, with emphasis upon physiotherapy, orthopedic appliances, adequate nutrition, relief of pain with analgesics, and more recently the use of thiamine chloride and the nicotinic acid derivatives. None of these measures has been adequate to control almost constant features of the disease: severe pain, muscle tenderness and hyperalgesia. The use of typhoid vaccine to induce fever in cases of this type was suggested in 1930 by Strauss and Rabiner [9] who administered it with good results in four cases, but they drew no definite conclusions because three other cases of a similar type recovered without the vaccine therapy. Mackay [10] mentions its use in one case without effect. Bennett [11] employed it in two cases of brachial plexus neuritis following administration of tetanus antitoxin and reported prompt and complete relief from pain. Individual cases were treated in a similar manner by Schneider [12] and Keschner [13] with good results.

Case Reports

Case 1. M. F., a waitress, aged 19, entered the Dermatologic Service, Kings County Hospital, February 26, 1946, for treatment of pediculosis and multiple cutaneous abscesses. Local therapy resulted in improvement. On April 11, 1946, she began to complain of numbness and weakness of the left extremities. Neurological examination two days later revealed mild weakness in all extremities with diminished to absent tendon reflexes, impaired sensation to pin and touch over the hands and forearm, especially on the ulnar aspect. An initial spinal fluid examination was negative except for total protein of 125 mg. per cent. All laboratory data were otherwise negative.

Upon transfer to the Neurologic Service, the patient was placed on intense vitamin therapy, but her progress was remorselessly downward for the next four weeks. She became almost completely quadriplegic with loss of sensation of a glove and stocking distribution. Facial asymmetry developed with flattening of the right nasolabial fold. Nasal speech and difficulty in swallowing ensued, and urinary retention with overflow incontinence occurred attributed to an atonic bladder as revealed by a cystometrogram. Calf muscle tenderness was severe. Spinal fluid protein remained at the same level.

Intravenous typhoid vaccine therapy was instituted on May 14. Two injections were given over a three day period, beginning with 10 million organisms and terminating with 30 million. Severe exacerbations of pain in the extremities occurred during the periods of temperature elevation. One day after this therapy was begun, for the first time in a month, there was a definite decrease in the deep muscle tenderness, with complete disappearance of this complaint in 14 days. Urinary incontinence ceased the day following the first typhoid injection. Motor power began to improve three days after therapy was instituted and continued, so that by June 14, one month later, the patient was out of bed and able to perform routine functions, and in another three weeks could walk unsupported. Sensation improved in less dramatic fashion but was almost normal within five weeks. The patient was discharged on August 2, at which time the only abnormalities were absent tendon reflexes, minimal hypalgesia of a glove and stocking type, and an atonic bladder.

Comment. This case presented a severe peripheral neuropathy with hyperalgesia so marked as to suggest radicular involvement. An albumino-cytologic dissociation

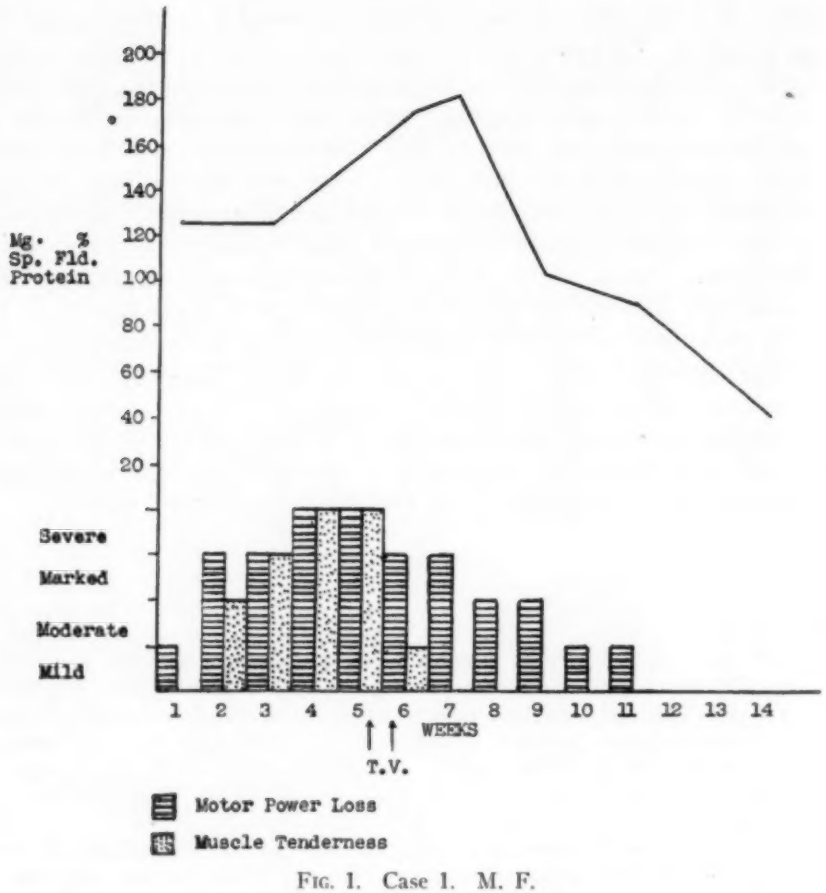

FIG. 1. Case 1. M. F.

was present. An unremitting downward progression was not affected by the usual supportive measures or vitamins, but recovery was initiated immediately after the institution of typhoid vaccine fever therapy.

Case 2. R. M., a garage attendant, aged 29, was admitted to the Neurologic Service on June 25, 1946, complaining of numbness, tingling and weakness of all extremities. Three weeks prior to admission he had a mild sore throat. One week later there ensued gradual tingling and numbness of the fingers and toes accompanied by weakness of the lower extremities, followed within two days by weakness in the upper extremities. This rapidly progressed to the stage where the patient could no longer kneel to lift a tire off a wheel. There was no excessive alcoholism, and the diet was adequate.

On admission the patient presented mild weakness of the upper and moderate weakness of the lower extremities, which were hypotonic, with absent tendon reflexes. Superficial sensory loss of a glove and stocking type was present, with position and vibration sense impaired in the lower extremities. The initial lumbar puncture was negative except for a faint Pandy reaction and a total protein of 49 mg. per cent. All laboratory studies, including throat cultures and Schick test, and urine studies for lead and porphyrins showed no abnormality.

The following four weeks, both motor and sensory disturbances advanced in severity and distribution, the former involving all the muscles of the trunk and ex-

tremities with atrophy of the forearms, hand muscles, thighs and calves. In addition, the patient developed hoarseness associated with weakness of the laryngeal abductors, some difficulty in swallowing, exquisite deep muscle tenderness, and occasional urinary incontinence which persisted despite intensive vitamin therapy.

Intravenous typhoid vaccine therapy was instituted on July 22. Six doses were given over a two week period, beginning with 10 million organisms and terminating with 100 million. Severe exacerbations of muscle pain were experienced with each temperature rise. Three days after inception of this therapy, the deep muscle tenderness was markedly diminished and was absent in 10 days. Urinary incontinence ceased. Motor power began to improve 18 days after beginning therapy and steadily improved, lagging mainly in movements of the ankles and toes. Sensory modalities improved within two weeks.

Upon discharge on August 12, there was minimal weakness in the extremities. Tendon reflexes were absent except for the biceps and triceps reflexes. Sensation was intact to pin prick and diminished to touch only over the toes, where position sense was also mildly impaired. Vibration remained impaired to the midtibial area. Follow-up examination two months later was completely negative neurologically but for impaired position sense in the toes and absent knee and ankle reflexes.

Comment. This case presented a severe peripheral neuropathy following an upper respiratory infection, with albumino-cytologic dissociation in all spinal fluid examinations except the first. There was an unremitting downward progression while on the usual supportive therapy. Fever induced with typhoid vaccine appeared to initiate an eventual complete recovery.

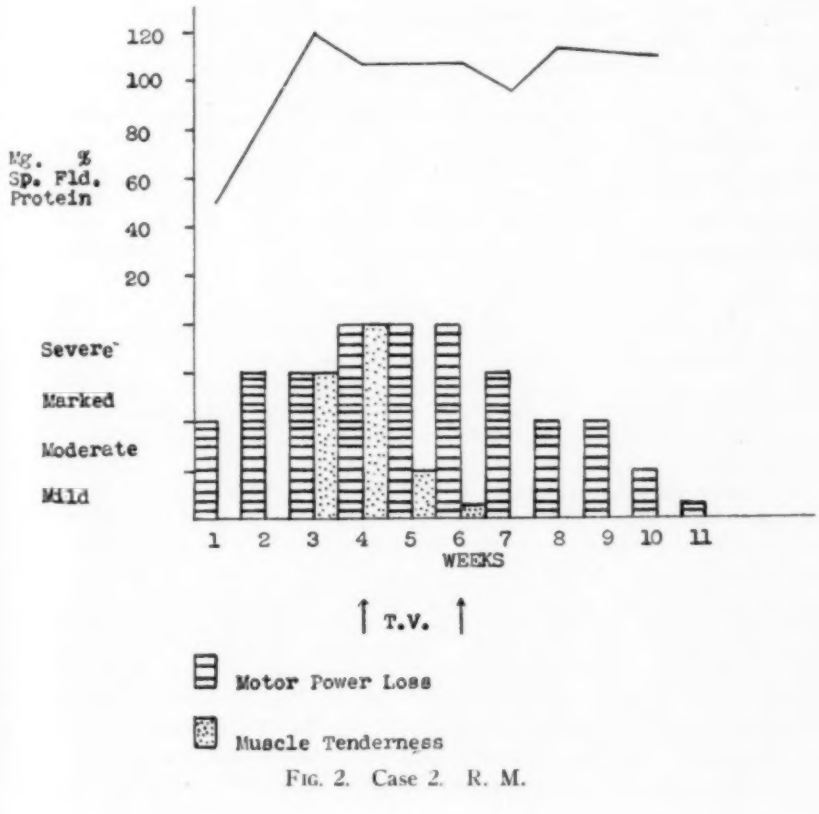

FIG. 2. Case 2. R. M.

FIG. 3. Case 3. J. H.

Case 3. J. H., a restaurant counterman, aged 40, was admitted to the Neurologic Service on November 14, 1946, complaining of tingling and numbness in all extremities. On September 20 he had developed pustular lesions of the left side of the face, head and neck following receipt of a blow with a broomstick. He entered the Dermatologic Service of another hospital on September 30, where local treatment resulted in improvement. Eight days later he first noted pins and needles sensations in the fingers. Within three days there occurred weakness of the upper extremities which rapidly progressed to involve all extremities, with diminution of reflexes. This rapid decrease in power developed while on heavy vitamin therapy. There was a history of moderate alcoholism, but the diet was adequate.

On admission to our service the patient presented marked weakness of all the musculature, most severe distally with atrophy of the hand muscles. The tendon reflexes were diminished in the upper and lost in the lower extremities. There was severe calf tenderness and plantar hyperesthesia, a glove and stocking type of sensory diminution with hyperalgesia of the fingertips. Touch appreciation was absent in the hands and in the lower limbs up to the inguinal area. Position sense was absent in both fingers and toes, with vibration impaired in all extremities. An initial lumbar puncture was normal except for a total protein of 51 mg. per cent. All laboratory data were negative, including urinary porphyrin studies.

During the first week of observation motor weakness became more severe, and deep muscle tenderness was exquisite. Intravenous typhoid vaccine therapy was instituted on November 21. Four injections were given over a 10 day period, with an initial dose of 10 million organisms and a final dose of 80 million. With each dose, severe exacerbations of pain in all extremities occurred, the severity decreasing with successive doses. One day, following institution of therapy, the patient volunteered the information that he "felt one thousand per cent better," and objectively showed a

marked diminution in muscle tenderness and plantar hyperesthesia, with a complete disappearance of these findings 11 days later. Motor power began to improve four days after typhoid therapy was begun and continued to improve gradually, with the greatest lag in the hand muscles and movement of the ankle and toes, finally permitting satisfactory performance of routine tasks three weeks later. All sensory modalities also showed improvement during this time. Examination 10 weeks after beginning therapy revealed mild weakness of the extremities, more marked distally, mild hyperalgesia over the fingertips, patchy areas of hypesthesia and hypalgesia over hands and feet, impaired position sense in the fingers with absence persisting in the toes, and vibration impaired up to the ankles. Only the biceps and triceps reflexes were present.

Comment. This case presented a typical picture of a peripheral neuropathy with slight increase in the spinal fluid protein, preceded by an acute scalp infection of unknown etiology. There was no response to the usual supportive and vitamin therapy. Immediately after the institution of typhoid vaccine fever therapy, muscle pain and tenderness disappeared. The return of sensation and motor power was more gradual.

Case 4. G. G., a nurse, aged 31 years, entered the Neurologic Service for her fifth admission on May 30, 1946. She complained of fever, redness and swelling of the left side of the face and forehead associated with a severe burning, tingling pain and numbness of the right side of the tongue. Previous pertinent history elicited the following: Her first admission occurred in September 1942 after contracting an upper respiratory infection following receipt of pertussis vaccine at a children's summer camp, where an epidemic suggestive of pertussis had occurred. At that time, findings of drowsiness, headache, girdle sensations, radicular pains, urinary incontinence, diplopia, bilateral fifth nerve involvement, right seventh and twelfth nerve involvement, weakness of the right arm and leg, a positive Babinski reflex on the left, and a right hemianalgesia and hemianesthesia had led to a diagnosis of acute encephalomyelo-radiculitis. She had improved following receipt of typhoid vaccine fever therapy. During the succeeding four years, repeated exacerbations occurred following upper respiratory infections, with symptoms similar to those on the original admission, although not as widespread and often involving other parts of the nervous system. Hospitalization was necessary in July 1943, February 1944, and January 1945. During the 1944 admission, typhoid vaccine fever therapy was given with very rapid recovery and again in 1945 with less prompt recovery.

On the present admission, positive findings included diminished sensation to pin and touch on the right side of the tongue, hyperalgesia with spots of hypalgesia over the ulnar aspect of the right forearm, spotty hypalgesia over the back of the right calf and thigh and exquisite pain along the course of the right ulnar nerve. Typhoid vaccine was given two days after admission with a temperature rise to 105° F., but no relief from symptoms occurred. Because of the constant history of an upper respiratory infection preceding each exacerbation, the patient was studied from an allergic point of view. A histamine phosphate sensitivity test resulted in a severe flare and wheal, followed in 15 minutes by an exacerbation of burning, itching and swelling of the left side of the face and in 30 minutes by a generalized urticaria. Desensitization was attempted with intravenous histamine phosphate, but the original symptoms remained unimproved. At the insistence of the patient, typhoid vaccine therapy was again instituted on June 15, and following one injection all symptoms abruptly subsided, leaving the patient only with hypalgesia of the left cheek, right side of the tongue, and along the distribution of the right ulnar nerve. She was discharged on June 19 and has since been receiving 0.5 c.c. of 1:1000 histamine phosphate twice weekly. Up to December 1946, she has had only two mild upper respiratory infections without neurological exacerbations.

Comment. This case presented at the onset a picture of an acute encephalomyelo-radiculitis following an upper respiratory infection and receipt of pertussis vaccine. She continued to have exacerbations in spite of almost constant vitamin therapy. No form of treatment offered the patient any relief except fever induced with typhoid vaccine. Although this was not always effective, the patient would come to the hospital requesting it when her symptoms were severe. The possibility of an allergic factor is suggested by her severe reaction to a histamine phosphate sensitivity test.

Case 5. M. S., a clerical worker, aged 35 years, who had also worked as a painter on and off for 15 years, entered the Neurologic Service on April 16, 1946, complaining of fever, attacks of hiccough and vomiting, radiating pains, and obstipation. Four months previously he had developed severe, intermittent, lancinating pain in the right lower back, which disappeared spontaneously in four days. Three months later similar pain developed in the left elbow, radiating down into the fourth and fifth fingers. In three weeks, it also occurred in the anterior left chest, and shortly thereafter in the anterolateral aspect of the right leg. No bowel movement had occurred for five days prior to admission, and hiccough and vomiting had begun two days before entry. There was no antecedent acute infection, no alcoholic history, and the diet was adequate.

On admission, the temperature was 101° F., the patient appeared acutely ill and was subject to bouts of hiccoughing and vomiting. The pains in the above described areas were of such exquisite intensity that bedsheets had to be kept away from the body by a cradle, and superficial sensation could be tested only with a cotton tip. The zones most severely involved were C4 to T4 and L1 to L2 on the left; less severely involved root zones were S1 to S3 on the left, and L2 to L3 on the right. Position sense was impaired in the left big toe, and vibration caused a burning dysesthesia in all extremities. There was mild hyperesthesia over the right side of the face. Slight paresis of the right lower extremity and marked paresis of the left lower extremity were present. The tendon reflexes were all hyperactive except for diminished triceps responses. The superficial abdominal reflexes were absent on the left and diminished in the right upper quadrant. An initial spinal puncture revealed a pressure of 240 mm. of water, but was otherwise negative. All subsequent lumbar punctures were negative except for a slight positive Pandy reaction on two occasions. Virus studies of the spinal fluid were negative. All laboratory data were within normal limits.

Two days after admission severe spasms of the calf muscles occurred. In spite of this development, the hiccoughing and vomiting receded and radicular pains lessened during the first week. Motor power began to improve in three and a half weeks. During the sixth week of hospital stay, further violent muscle spasms occurred, involving a greater amount of the musculature than previously. A Babinski and a Chaddock sign developed on the left. During the ninth week an episode of blurred vision occurred for half an hour. This was repeated a week later, but persisted, and a horizontal nystagmus was also present. Atrophy of the left hypothenar eminence with occasional fibrillations was noted. During the tenth week the bouts of hiccough and vomiting recurred, and the patient complained of numbness of the left side of the face. A complete left sided hypesthesia, hypalgesia and thermhypesthesia was found, most marked from T10 to C4. The right pupil was smaller than the left. There were bilateral positive Babinski signs.

On July 14 intravenous typhoid vaccine therapy was begun. A total of five injections over a 12 day period was given, starting with 10 million organisms and terminating with 200 million. One day after this therapy was begun the patient showed subjective improvement and lessened frequency of muscle spasms. Superficial sensation on that day was normal except for mild hyperesthesia of the right

side of the face and ulnar aspect of the left palm. These were the most minimal sensory disturbances since the patient's admission. A gradual recovery of motor power was evident shortly after this therapy and continued until the patient signed his release on August 3. On that day the residual findings were a coarse horizontal nystagmus on forward gaze, mild hyperesthesia of the right side of the face and ulnar aspect of the left palm, minimal paresis of the left lower extremity, generally hyperactive reflexes except for the triceps, absent abdominal reflexes, and occasional bilateral positive Babinski signs. Position sense was impaired in both big toes and vibration sense was diminished bilaterally up to the iliac crests.

Comment. This case presented an acute encephalo-myelo-radiculitis with consistently normal spinal fluid. Although there were periods of recession of symptoms, exacerbations were characterized by increasing sensory involvement and a greater amount of musculature involved in the spasms which so distressed the patient. We believe that the improvement following typhoid vaccine fever therapy was too prompt and sustained to be purely coincidental, although we hesitate completely to attribute the patient's partial recovery to this form of therapy.

Case 6. E. J., a housewife, aged 52 years, entered the Neurologic Service on December 5, 1946. On December 2 she had awakened from sleep with wheezing and tightness in the chest. Within 12 hours, vertigo, severe suboccipital headache, anorexia and generalized weakness ensued. On December 3, she could not close either eye, and the right side of her face felt "drawn up." This was followed by pins and needles sensations in all extremities and knifelike pain in the upper back, radiating anteriorly to the chest and abdomen. Paresis of both legs followed, then difficulty in starting the urinary stream, and finally transient diplopia.

On admission she presented a facial diplegia, moderate paresis of extension of both arms and weakness of both lower extremities. The tendon reflexes were absent except for a left biceps response, and a right positive Babinski with an equivocal left Babinski was noted. Cerebellar ataxia on the right finger to nose test was found. Superficial sensation was diminished below T6, most marked from the knees down. Sensation was also disturbed in both hands. Position sense was absent in both big toes, with vibration appreciation impaired to the costal margins. The patient spoke in a slurred manner and had difficulty in swallowing, although movement of the uvula and palate was normal. The initial lumbar puncture revealed a two plus Pandy reaction, two lymphocytes, and 77 mg. per cent of total protein. The white blood cell count was 14,000 with a normal differential. All other laboratory data were normal.

The patient became progressively worse, with more generalized shooting pains, increasing weakness, and transient periods of urinary retention followed by incontinence of both feces and urine. Bilateral fifth nerve disturbance developed, while deep muscle tenderness and plantar hyperesthesia became severe. Intravenous typhoid vaccine therapy was instituted on December 14, with an initial dose of 10 million organisms requiring a stepup dose of an additional amount because of a poor temperature response. Three injections over a five day period were given, with a final dose of 50 million organisms. On December 15, one day after this therapy was begun, the patient stated she had marked relief from her girdle pains and that she had not felt as well since the onset of her illness. She could now control rectal functions. The sensory level showed a sudden drop to T12, below which it was much less marked than on admission. Motor power and calf muscle tenderness remained unchanged, but there was no further progression of paresis. Two days later there was definite improvement of power in the distal musculature of the lower extremities. However, on December 18 calf muscle tenderness became more severe and an exacerbation of radicular pains occurred. On December 20 the patient was found in shock and died in a few hours. Autopsy revealed an aspiration pneumonia with atelectasis.

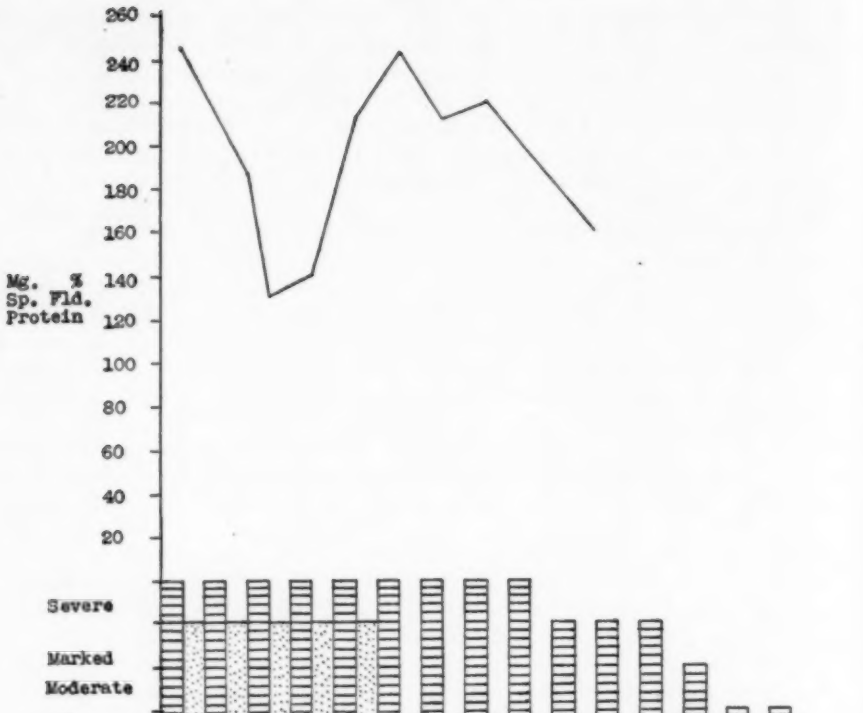

FIG. 4. Case 7. R. Mn.

Comment. The unfortunate sudden death of this patient, who presented signs of an encephalo-myelo-radiculo-neuritis, prevents any accurate evaluation of her response to typhoid vaccine fever therapy. There was definite recession of the sensory level from T6 to T12 and arrest of fecal incontinence within 24 hours after beginning the fever therapy.

Case 7. R. Mn., a drifter, aged 39 years, entered the Neurologic Service on October 15, 1946, complaining of weakness and muscle aching. Five weeks previously he had chills and fever for several days, followed in one week by burning sensations in the soles of the feet and weakness of the ankles. Thereafter, progressive involvement of all the muscles and cramping pains in the calves developed. Up to four months prior to hospital entry, he had been a heavy drinker with a poor dietary intake.

On admission, he appeared chronically ill. The lingual and cutaneous changes suggested avitaminosis. The pupils were irregular, unequal and reacted poorly to light. Severe weakness of all the muscles, with partial wrist and foot drop, was

noted. Only a left triceps reflex was elicited, a glove and stocking type of hypalgesia and hypesthesia was present, most marked distally, with vibratory appreciation absent up to the elbows and position sense absent in the fingers and toes. Laboratory data revealed a mild secondary anemia, an increased sedimentation rate, with urinalyses negative for lead and porphyrins. The spinal fluid was under normal pressure, with five polymorphonuclear leukocytes and five lymphocytes, a total protein of 254 mg. per cent, sugar 76 mg. per cent, and chlorides 704 mg. per cent. The colloidal gold curve was 4454332100, and both blood and spinal fluid Wassermann reactions were four plus.

Heavy vitamin therapy for one month resulted only in the improvement of the patient's sense of general well being. Repeated spinal fluid studies showed a rising cell count up to 65 lymphocytes and a decrease in total protein to 133 mg. per cent. Intravenous typhoid vaccine therapy was instituted on November 19. Four injections were given over an eight day period, beginning with 10 million organisms and terminating with 80 million. With each paroxysm of fever, a severe exacerbation of calf muscle tenderness occurred, diminishing in intensity with each successive dose.

On the day following the first injection, the patient felt subjectively better with complete disappearance of deep muscle tenderness. The only other improvement was somewhat less extensive glove and stocking sensory disturbance. Laboratory data indicated syphilis as at least co-existent with the presenting disturbance, and penicillin therapy was instituted on December 15, the patient receiving 50,000 units intramuscularly every three hours. One week later, after having received two and a half million units (and one month after the fever therapy was begun), the patient showed a surprising sudden improvement. Motor power had increased throughout, even in the hand muscles and at the ankles and toes. By December 24 there was no longer any wrist drop, and the patient had improved. He could now wash and feed himself. The glove and stocking distribution of sensory loss had diminished markedly, with touch now perceived, although diminished, over the hands, absent in the feet, and diminished to the knees. By mid-January he was walking about the ward with slight support. The tendon reflexes were still absent. Pin and touch sensation were unimpaired in the upper extremities and only mildly impaired in the lower extremities up to the ankles. Position sense was present in the fingers but impaired in the toes. Vibratory appreciation was intact.

Comment. This patient presented a severe peripheral neuropathy, with increased cells and protein in the spinal fluid. This illness followed a febrile episode but was complicated by the presence of neurosyphilis. Supportive therapy offered no relief, but immediately following typhoid vaccine therapy pain and muscle tenderness disappeared. Return of motor power was delayed until after the administration of penicillin. Evaluation of the effect of the latter therapy on the course of recovery is difficult because of the short interval between the beginning of its administration and the return of motor power.

Discussion

This report is limited to an evaluation of the use of fever therapy induced by the intravenous injection of typhoid vaccine in cases which can best be included under the general classification of acute infectious neuronitis or neuronopathy. TAB vaccine was used, but only the number of typhoid organisms was counted. The dosage schedule depended upon the febrile response and clinical reaction of the patient. The initial dose was 10 million organisms. If little or no response was obtained to the first dose, a stepup dose of the same amount was given within a few hours. Increasingly larger

doses were given every second to third day, and on intervening days salt, fluids and plasma were given as indicated. Febrile responses varied from 101° to 105° F. A consistent response in all patients except Case 5 was severe exacerbations of pain in the extremities during the febrile phase. So constant was this finding that it seemed to indicate that an effect was being obtained, and treatment was discontinued when it no longer occurred. In spite of the extreme discomfort of the patients during the treatment, their relief from pain was so gratifying that they themselves often requested further injections.

Not infrequently, in similar cases, spontaneous recovery after varying intervals of time is observed and, therefore, conclusions as to any form of therapy can by no means be dogmatic and absolute. However, among the cases observed on our Neurologic Service, we sought to choose only those whose course appeared to be constantly downward in spite of all the usual supportive therapy. Cases 1, 2, 3, 6, and 7 showed increasing muscle tenderness, loss of motor power and sensory diminution. Case 4 had repeated exacerbations over a four year period. Case 5 showed progressive involvement of the musculature in severe spasms, and marked advance in sensory disturbance.

Of the seven patients, six improved following typhoid vaccine fever therapy. Case 6 died before reliable evaluation was possible, the cause of death being aspiration pneumonia with atelectasis. Case 7 showed rather late improvement after the fever therapy but too rapid improvement after penicillin therapy to attribute it entirely to the latter drug. The nature of the improvement is considered in four categories.

(*a*) *Relief of Pain.* This was the most dramatic feature of the therapy. The muscle tenderness was reduced to a minimum within 24 to 48 hours after the first injection, was usually completely absent within a week, and did not recur. Once the pain was relieved, the patients would acquire a sense of well being and give up their usually pessimistic attitude toward their illness. The relief from pain and tenderness also permitted the earlier institution of physiotherapeutic procedures.

(*b*) *Recovery of Motor Power.* This lagged behind the relief of pain and was present in cases 1, 2, 3, and 4. The return of power in case 5 following vaccine therapy was no greater or more rapid than it had been during previous remissions, although it was maintained much longer. Case 6 died before accurate evaluation was possible, but the advancement of paresis appeared to have ceased following typhoid vaccine. Case 7 showed recovery of motor power beginning 30 days after vaccine therapy was instituted and seven days after penicillin was begun.

(*c*) *Recovery of Sensation.* Sensory recovery following typhoid vaccine therapy was inconstant and variable and usually the last to respond, except in cases 5 and 6. Case 5 displayed a return of sensation following the first injection of typhoid vaccine that was as dramatic as the relief of pain in the other cases. Case 6, who had a sensory level at T6, showed a

regression of this level to T12 almost immediately. In most of the patients a return of superficial sensation was heralded by the appearance of patchy areas of hyperesthesia and hyperalgesia in the previously involved areas, but these were never very disturbing to the patient.

(*d*) *Spinal Fluid Changes.* No correlation existed between the severity of the illness, the downward course and the final recovery on the one hand, and the spinal fluid protein on the other. Case 5 had a normal spinal fluid throughout. Case 4 showed normal spinal fluids from 1942 to 1946. Case 1 showed decreasing spinal fluid protein during recovery, whereas cases 2, 3, and 7 maintained a high spinal fluid protein even during the recovery phase.

The basis of the favorable response to fever induced with typhoid vaccine remains obscure. The numerous explanations offered are an indication of the lack of positive evidence as to exactly what occurs. It has been suggested that the elevated body temperature creates an unfavorable environment for the pathogenic organism concerned. This does not seem likely in several of our cases where a good response was noted with only a minimal rise in temperature. Other speculations concern themselves with the blood supply, implying that an increased vascular flow occurs peripherally in inflamed areas, increasing oxidation and nutrition, furthering dilution of toxins and healing of inflamed tissue. Still a third suggestion concerns itself with the body's general cellular and glandular responses because of leukocytosis, phagocytosis and enhanced antibody formation, all resulting in a better mobilization of the entire system of tissue defense.

Summary

1. Seven cases of acute infectious neuronitis or neuronopathy have been presented and their response to fever induced by typhoid vaccine evaluated.

2. The method of typhoid vaccine fever therapy has been outlined.

Conclusions

The favorable response of six of seven patients to typhoid vaccine fever therapy indicates that further intensive trial with this form of therapy in acute infectious neuronitis or neuronopathy is indicated.

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PRIMARY SPLENIC NEUTROPENIA WITH ARTHRITIS (SO-CALLED FELTY'S SYNDROME). ITS TREATMENT BY SPLENECTOMY *

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In 1924 Felty [1] described the syndrome of chronic rheumatoid arthritis associated with splenomegaly and leukopenia. He was preceded by Still [2] who, in 1897, reported a disease of children characterized by chronic joint disease, splenomegaly and leukocytosis. In 1932 Hanrahan and Miller [3] performed the first splenectomy for Felty's syndrome. The operation was done primarily to relieve the patient of the discomforts of the enlarged spleen and to correct the leukopenia. What reasoning led them to expect the latter is obscure. Because of the good result obtained by Hanrahan and Miller, Craven [4] carried out the same operation in his patient in 1934. However, it remained for Steinberg [5] in 1942 to note for the first time the bone marrow hyperplasia in two such cases and to suggest that the spleen might be inhibiting the maturation of the granulocytes. He further stated that "if inactivity of the bone marrow is present splenectomy should not be done."

In 1939 Doan and Wiseman [6] reported three cases of "a newly recognized granulocytopenic syndrome with the bone marrow showing myeloid hyperplasia of qualitatively normal cells." Splenomegaly and profound leukopenia were present. There was no evidence of liver disease, chronic infection or other factors that might produce this picture. None had any recognizable arthritis. All of these patients were cured by splenectomy, and there was a prompt reëstablishment of a normal peripheral leukocyte count. The spleens all showed histologically excessive phagocytosis of the granulocytes.

In 1939 Moore and Bierbaum [7] and in 1941 Muether et al.[8] reported two more such cases which were cured by splenectomy. Doan and Wiseman [9] in 1942 added two more cases to their original group and named the syndrome primary splenic neutropenia. They compared it to congenital hemolytic icterus and essential thrombocytopenic purpura. They stated that all of their cases have the "common denominator" of profound granulocytopenia, panhyperplasia of the bone marrow, enlarged spleen, and cure by splenectomy. In addition there were also present varying degrees of anemia and thrombocytopenia which were asymptomatic and which were coincidentally corrected by removal of the spleen. These investigators felt that a single mechanism was responsible for the varying degrees of anemia, neutropenia and thrombocytopenia in this group of cases. The spleens all showed excessive phagocytosis of granulocytes, red cells and platelets. They concluded that the syndrome is due to a "hypersplenism" in which there is an

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accentuation of the physiologic function of disposing of blood cells and that it is comparable to congenital hemolytic icterus and essential thrombocytopenic purpura. In the former disease the phagocytic activity of the spleen is directed chiefly against the red blood cells; in the latter, chiefly against the platelets; and in the neutropenic syndrome chiefly against the granulocytes.

Furthermore, Doan and Wiseman did not believe that Felty's syndrome could be either included or excluded from this neutropenic syndrome because of the limited data available.

In 1945 these same investigators [10] first used the term splenic panhematopenia for the picture in which the enlarged spleen is associated with a marked and usually symptomatic decrease in all the cellular elements of the blood. They described several such cases. They felt that in this syndrome the spleen fails to discriminate between the blood cells passing through it, and that there results a peripheral blood picture and clinical picture resembling the complete marrow hypoplasia seen in aplastic anemia. In these cases the bone marrow showed hyperplasia of all the normal elements without pathological maturation arrest or significant qualitative abnormalities. These patients were also cured by splenectomy.

With this background in mind we wish to present two cases showing chronic neutropenia, splenomegaly and advanced arthritis. The first case showed a hypoplastic bone marrow, some anemia and thrombocytopenia, and the second a hyperplastic bone marrow with no anemia or thrombocytopenia. Splenectomy was followed in both by a return of the blood pictures to normal and marked clinical improvement in the patients' health.

Case Reports

Case 1. W. C. T., a white male of 52, salesman, was treated at another local hospital in February 1941 for pneumonia of the right middle lobe. In addition to the pulmonary changes, examination revealed enlargement of the spleen, anemia and leukopenia (table 1). The pneumonia cleared up on sulfapyridine therapy, but the anemia, splenomegaly and leukopenia persisted. Diagnoses on discharge were pneumonia and splenomegaly with blood dyscrasia (unexplained).

On May 10, 1946 we first saw the patient when he was admitted to the Mercy Hospital because of weakness and loss of 15 pounds since January 1946. He stated that "everything I do is an effort and I always feel as if I needed sleep."

Past history revealed repeated infections. In 1909 he was hospitalized for nine months for pulmonary tuberculosis. Chronic rheumatoid arthritis had been present since 1921. He had had gonorrhea twice, the last time about 1930. Cellulitis of the dorsum of the left foot occurred in 1936. He had had pneumonia in 1941, pleurisy in 1942, and pneumonia again in December 1945. There had been no exposure to any drugs or chemicals.

Examination revealed an elderly looking, gray-haired man appearing older than his stated age and weighing 143 pounds. He was somewhat pale, with dark brown pigmented macular areas around the ankles and extending a short distance up both legs. There was complete adentia (artificial plates). The heart and lungs were negative. The blood pressure was 105 mm. Hg systolic and 90 mm. diastolic. The

TABLE I

Date	Hgb %	Hgb gm.	R.B.C. millions	W.B.C.	Juv.	Stab.	Poly.	Lymph.	Mono.	Platelet	Retic.	Fragility	Coag. Time	Bleed. Time
											%			
1–20–41	63		2.67	3,300		6	62	17	4				3′	1′
1–23–41	70		3.55	3,600			79	15	6				1′	10′32″
5–11–46	64	9.6	3.58	1,350			25	65	10					
5–12–46	69	10.5	3.59	2,275			21	73	6	113,660	0.6	0.4–0.3		
5–18–46	Folic acid begun, 5 mg. 4 times daily													
5–22–46	72	10.8	3.550	1,250		7	22	54	15	153,720	2.0			
5–25–46	76	11.5	3.960	1,200		11	23	51	11	134,640	4.0			
6–24–46	74	11.4	3.83	1,450			40	60		375,340	2.0	Folic acid stopped		
Before adren.														
6–27–46	52	7.9	3.85	1,600		4	12	81	2	225,610				
After adren.														
6–27–46	72	10.7	3.76	2,250		3	14	80		298,200				
6–29–46	77	11.8	4.03	1,550		4	12	76	6	298,400		2 hours before operation		
Splenic artery														
6–29–46	100	15.0	4.81	3,400		3	12	80		371,100				
Splenic vein														
6–29–46	76	11.4	3.71	2,850						298,000				
6–29–46	78	11.8	3.80	2,450		11	43	45		380,000		1 hour after operation		
6–30–46	90		4.48	10,300	10	32	50	6	2	407,600				
7–5–46	68	10.3	3.67	7,250		69	66	24		528,480	0.3			
7–10–46	73	11.1	3.950	9,250		11	51	35	3	948,600				
11–3–46	106	16.5		6,380										

spleen was enlarged, extending to the umbilicus. There was no enlargement of the liver, no ascites, and no evidence of collateral circulation. There were marked arthritic deformities of the wrists and of the fingers of both hands, with ulnar deviation, and moderate changes in the knee joints.

Roentgenographic studies of the chest and gastrointestinal tract were negative. No esophageal varices could be demonstrated. Roentgenograms of the joints showed extensive rheumatoid changes of the bones of the hands and wrists and minimal changes in the knees. The electrocardiogram was normal.

TABLE II

Sternal Marrow of Case 1 in Comparison with Steinberg's [5] Hyperplastic Marrow and Normal Marrow from Wintrobe

	May 14	June 27	July 9	Steinberg	Wintrobe
Myeloblasts	0.0	0.6	0.0	7.0	2.0
Promyelocytes	0.2	1.8	1.0	9.0	5.0
Myelocytes	4.2	5.8	2.8	10.0	12.0
Juveniles	6.0	8.8	5.0	7.0	22.0
Staff	16.6	16.8	21.2	8.0	
Polym. Neut.	7.4	5.0	33.4	12.0	20.0
Polym. Eosin.	2.4	1.0	4.4	1.0	2.0
Polym. Basoph.	0.0	0.0	0.0	0.0	0.2
Prolymphocytes	0.6	1.8	0.4	8.0	
Lymphocytes	22.0	33.0	24.0	6.0	10.0
Monocyte	1.2	0.4	2.0	2.0	2.0
Megaloblast	1.6	0.0	0.2	3.0	
Erythroblasts	8.6	7.6	1.0	9.0	4.0
Normoblasts	28.6	16.6	4.4	16.0	18.0
Tissue cells	0.6	0.8	0.2		0.2
Megakaryocytes		0.2			0.4
Plasma cells				2.0	0.4
Comment:—	Hypocellular, granulopenic but normoblastic.	After folic acid.	Post op. granulocytes increased.	Hyperplastic.	Normal.

The successive blood counts are presented in table 1 and the bone marrow studies in table 2. Other laboratory data were as follows: gastric analysis showed relative hypochlorhydria with a prolonged rise, serum proteins 8.1 per cent, albumin 4.1 per cent, globulin 4.0 per cent, vitamin C level 0.7 mg. per cent, cephalin flocculation 2 plus in 48 hours, prothrombin clotting time (undil.) 19 seconds, (dil.) 67 seconds, icteric index 5.2, van den Bergh 0.5 mg. Blood sugar and urea were normal. Serologic test for syphilis was negative. Bromsulfalein test of liver function showed 4 per cent retention in 60 minutes. Hematocrit 38 per cent, clot retraction was complete in 12 hours, bleeding time was one minute, coagulation time was 10 min. 32 sec. Gothlin index normal, urine contained 0 to 2 plus albumin, no sugar; urobilinogen was present.

The bone marrow studies (table 2) were interpreted by Dr. H. R. Peters, hospital hematologist, as follows: preoperative marrow, May 14, 1946, "normoblastic marrow in the sense that in this relatively hypocellular marrow the normoblasts are actually increased. It is not a hyperplastic marrow. No abnormal cells are seen. Would be compatible with any leukopenic blood dyscrasia, primary splenic neutropenia, so-called Felty's syndrome, Hodgkin's of the spleen, etc."

There was no change in the patient's condition or blood picture during this first Mercy Hospital admission. He was discharged on May 19 after nine days in the hospital, and at this time began to take folic acid 5 mg. four times daily which he continued to take until June 24, 1946, the day of the second hospital admission. Blood counts were made several times weekly while on this medication, except for a lapse of one entire week. As shown in tables 1 and 2 the main features of the blood and bone marrow studies were the presence of a marked leukopenia and granulocytopenia, a moderate anemia and thrombocytopenia, and a hypoplastic bone marrow.

On readmission to the hospital the most relevant blood studies were repeated, together with another sternal puncture to see what effects, if any, folic acid had produced. No change was noted in the blood picture except a moderate increase in the number of platelets.

On June 29, 1946 a splenectomy was performed by Dr. Walter D. Wise. At the operation the liver appeared grossly normal and the splenic artery and vein were much dilated. The splenic vein was not thrombosed. The spleen weighed 1446 grams, measured 8.5 by 6 by 3.5 inches, and was fairly soft. Smears taken from the pulp of the freshly removed spleen and stained with Wright's stain showed no unusual phagocytosis (supravital stains not made).

Microscopic description of the spleen by Dr. Walter C. Merkel, hospital pathologist, was as follows: "The malpighian bodies are well preserved, the germinal follicles are hypertrophied. The sinusoids are markedly dilated and engorged with red cells. The reticulum is reinforced by fibroblasts; there is no patchy fibrosis. There is a moderate amount of free pigment; an occasional large phagocytic cell is encountered which also contains pigment. There are no polys; the predominating cells are lymphocytes. Plasma cells are relatively numerous. The capsule is thickened, trabeculations are hypertrophied. There is no hemorrhage, no infarction, and no accumulation of pathological leukocytes. There is nothing to suggest neoplasm." Pathological Diagnosis: Splenomegaly characterized by hypertrophy of malpighian bodies and hyperemia. Compatible with Felty's syndrome. The conditions which can be ruled out are Hodgkin's, Banti's syndrome, and the leukemias.

The adrenalin test done before splenectomy showed an increase in the leukocytes from 1600 to 2200 with no change in per cent of granulocytes. Postoperative marrow July 5, 1946 (table 2): "Marrow still grossly hypoplastic. The only change from previous smear is a slight increase in granulocytes. The erythroblastic elements are proportionately less than before splenectomy."

The patient withstood the operation well and was discharged 17 days later. The improvement in his blood count is shown in table 1. He was last seen on November 14, 1946 at which time he had gained 20 pounds in weight and stated that he felt stronger, had more pep, and was able to do much more work than he had done for years.

Case 2. This patient, a 59 year old white female, was first seen by her family doctor about March 15, 1945, complaining of an ulcer on the lateral aspect of her left ankle which had been present for six months. In addition she also had symptoms and signs of arthritis in both shoulders, elbows and knees, which she stated had been present for four years. Attention was directed primarily to the ulcer which was treated with Unna's paste bandage, tyrothricin and warm compresses at different times for three weeks without success. A complete examination then revealed an enlarged spleen and a low leukocyte count (table 3), and the patient was admitted to the Mercy Hospital on April 14, 1945 for further study.

In the hospital, in addition to the leg ulcer and the arthritis, the patient complained of general malaise, anorexia, fatigue and soreness of the tongue. There had been a loss of 75 pounds since the onset of the arthritis. The past history revealed

TABLE III

Date	Hgb		R.B.C.	W.B.C.	Stab.	Seg.	Lymph.	Mono.	Eos.	Platelet	Ict. Index	Van den Bergh	Fragility
	%	gm.											
4–7–45	82	11.8	4.990	2,500		10	56	9	22				
4–13–45				1,850	10	7	47	6	30			0.4	
4–16–45	87	13.7	4.800	1,800	2	10	58	2	28	556,800	10	Indirect	
4–18–45				1,400	2	8	56	2	32				0.4
4–23–45	85	12.9	4.12	1,500	2	10	58	2	28				0.25
5–2–45	86	13.0	4.45	1,500	2	14	54	2	28				
5–9–45	97	14.7	4.65	1,400	6	14	60	6	14				
Post-op.													
5–23–45	97	14.6	4.83	11,050	32	29	37		2	589,000			
5–24–45				11,150	42	34	20	2	2				
5–25–45				7,600	16	33	24	7	20				
5–26–45				8,200	12	9	25	1	53				
5–28–45	92	13	4.47	5,050	14	28	26	1	31	713,200			
6–2–45	96	14.5	4.63							1,259,600			
6–4–45				6,400	11	19	36		34				
6–5–45	90	13.6	4.70							1,205,760			
6–7–45				6,900	13	8	27	12	40				
6–12–45	90	13.6	4.7	6,100	11	7	46	30	6	989,100			
6–14–45	90	13.6	4.7										
8–5–45	96	14.5	4.35	13,800		68	26		6				

pneumonia and influenza in 1919. Menopause began at 53. There had been 13 pregnancies but several of these had miscarried. Family history was noncontributory.

Physical examination showed evidence of much weight loss, the weight at this time being 138 pounds. Small tophi were present in the left ear lobe, lenticular opacities in both eyes, and artificial plates in both jaws. There was slight cervical adenopathy. Blood pressure was 122 mm. Hg systolic and 72 mm. diastolic. The heart and lungs were normal. The spleen was felt 3 cm. below the left costal margin. The liver could not be felt. Many subcutaneous, pea to olive size nodules were palpated over the different joints. On the lateral aspect of the left ankle there was an ulcer the size of a half dollar covered by a thin crust. The skeletal system showed marked kyphosis of the thoracic portion of the spine with arthritic deformities of the toes and fingers. Crepitus was present in both shoulders. There was marked limitation of motion of all the larger joints, with flexion deformity of the elbows and hands.

Roentgenograms of both hands showed atrophy of the bones and some soft tissue swelling around several interphalangeal joints. Roentgenograms of the dorsal spine revealed postural deformity with hypertrophic arthritis.

Study of the blood presented essentially a persistent granulocytic leukopenia with a marked eosinophilia (table 3). Bone marrow smears from sternal puncture showed an increase in the young granulocytes (hyperplasia) and an increase in the eosinophiles of all stages of maturity (table 4). Interpretation by Dr. H. R. Peters, hospital hematologist, was that it was not a "leukemic marrow, even a so-called eosinophilic leukemia."

Other laboratory data were as follows: urine was negative; total protein 5.9 per cent, albumin 3.4 per cent, globulin 2.5 per cent, albumin-globulin ratio 1.3; blood sugar 83 mg. per cent, urea 18 mg. per cent, uric acid 2.4 and 4.0 mg. per cent; hippuric acid 86 per cent excretion, bromsulfalein liver function 3.2 per cent retention in

TABLE IV

Sternal Marrow, Case 2

Blast		6.2%
Myeloblast		
Premyelocytes	Neutrophilic	7.4%
	Eosinophilic	5.4%
Myelocytes	Neutrophilic	12.2%
	Eosinophilic	5.2%
	Basophilic	
Juvenile		12.6%
Staff		9.2%
Polymorphonuclears:	Neutrophilic	2.2%
	Eosinophilic	10.0%
	Basophilic	
Prolymphocytes		
Lymphocytes		12.4%
Megakaryocytes		
Plasmocytes		
Megaloblasts		
Erythroblasts		10.8%
Normoblasts		5.2%
Mitotic figures		0.4%
Unclassified		0.6%
Tissue cells		0.2%

Comment: Increase in immature myeloid cells with decrease in mature myeloid cells.

60 minutes; cephalin flocculation 4 plus in 24 hours. van den Bergh indirect reaction 0.4 mg. per cent; icteric index 10. Serologic test for syphilis was negative.

Biopsy of one of the subcutaneous nodules taken from over the olecranon process showed "necrosis, scarring and probable foreign body reaction, with no evidence of trichinosis."

Because of the leukopenia, enlarged spleen, and the evidence of hyperplasia in the bone marrow it was decided that splenectomy should be done, and accordingly operation was performed on May 22, 1945 by Dr. Patrick Phelan.

The spleen measured 18 by 11 by 6 cm. and weighed 600 grams. It was soft. Microscopically (C. G. Warner, Hospital Pathologist) the capsule was found to be thickened, the malpighian bodies were small and numerous and the pulp appeared both cellular and fibrous. It showed a rather non-specific histopathological picture, that is, "it is compatible with a number of different entities, and the diagnosis is not evident on histopathological examination alone."

The patient withstood the operation well. Blood counts subsequently showed a return to normal of the total number of leukocytes, but the eosinophilia persisted (see table 3). On June 16, 1945 the patient was discharged and was never seen again by us, having returned to her home in Tennessee.

On August 24, 1946, we received the following communication from her physician, Dr. P. J. O'Brien in LaFollette, Tenn. "The patient weighs 155 pounds, is ambulatory and still complains of her arthritis but not so much as previously. The ulcer on her ankle, although still present, is smaller, about the size of a quarter, with smooth edges. Her blood count is: hemoglobin 95 per cent, red blood cells 4,350,000, white blood cells 13,000, polymorphonuclear leukocytes 64, large lymphocytes 10, small lymphocytes 12, basophiles 8, eosinophiles 6. Platelet count was not done. From her history I think she has made a marked improvement."

DISCUSSION

Our first patient, who has had arthritis for 21 years, has it now in an advanced stage. He has had repeated infections. Anemia, splenomegaly, and leukopenia have been present for at least five years. It is probable that the

thrombocytopenia has been present for this length of time also, but unfortunately, platelet counts were not done during his first hospitalization in 1941.

In presenting our cases we are not concerned with entering into the discussion as to whether we should label them as cases of so-called Felty's syndrome or, by considering the arthritis merely a coincidence, to classify them with the cases of primary splenic neutropenia which were first described by Doan and Wiseman.[6] Singer and Levy,[11] Talkov, Bauer and Short,[12] and Steinberg [5] have given good discussions of this question. Dameshek [13] believes that "Felty's syndrome is a form of splenic leukopenia due to involvement of the spleen in the chronic infectious or toxic process of the rheumatoid arthritis."

In regard to the mechanism of production of the leukopenia or pancytopenia our cases appear to lend no support to the theory of Doan and Wiseman [6] that the blood cells undergo "sequestration" and phagocytosis by the hyperactive and enlarged spleen; first, because our spleens showed no unusual phagocytosis and secondly, because the anemia which was present in our case 1 was not hemolytic in type. However, it should be mentioned that these investigators state that supravital stains are necessary to demonstrate phagocytosis in the spleen. Such stains were not made in our cases.

Dameshek [14] favors the hypothesis that the enlarged spleen inhibits the blood cells of the bone marrow from either maturation or liberation into the blood stream by means of splenic hormones. We have no evidence in our study for or against this theory. In spite of the disagreement as to its mechanism the proponents of both schools of thought agree as to the reality of the syndrome and the effects of splenectomy.

Our first patient (case 1) differs somewhat from those described by Doan in that the bone marrow was hypoplastic rather than hyperplastic. This absence of hyperplasia gave us much concern regarding the advisability of splenectomy since we feared that the removal of the spleen would be of no avail in the face of what appeared to be a poorly functioning bone marrow. Doan,[6] Muether,[8] and Steinberg [5] all stress the importance of having a hyperplastic bone marrow before subjecting the patient to splenectomy. It is worthy of note that Hanrahan and Miller [3] and also Craven [4] had previously performed splenectomy on their patients without bone marrow biopsies (marrow biopsies being a fairly new procedure at the time). Steinberg,[5] as previously stated, was the first to remove the spleen in so-called Felty's syndrome knowing that the bone marrow was hyperplastic and suggested that there was an inhibition of cell maturation.

In our review of the literature of this subject we could find only four cases which did not show bone marrow hyperplasia. In two of these the marrow was described as normal and in two as hypoplastic. Salzer, Ransohoff and Blatt [22] and Alt [10] reported those with normal marrows which responded to splenectomy with return of the blood pictures to normal. Wil-

liams' [16] case, in which the bone marrow was obtained at autopsy, showed a diminution in granulopoiesis. No splenectomy was done. In the three bone marrow specimens of Moore's patient [7] taken before splenectomy there was relative acellularity which suggested moderate hypoplasia. Here there was an increase in cellularity following operation and all the cellular elements of the peripheral blood returned to normal.

The adrenalin test [15] is considered by Doan and his school as a helpful diagnostic test in deciding on operation. If there is a significant rise in the neutrophiles after the hypodermic injection of adrenalin they feel that the spleen is incriminated in the neutropenic syndrome. Lucia, Leonard and Falconer [17] have shown, however, that adrenalin causes an increase in the peripheral granulocytes even in splenectomized patients. They also state that adrenalin does not stimulate the bone marrow, and they conclude that the test is of no diagnostic value. In our first patient there was a small rise in the total leukocyte count with no change in the differential picture. For these reasons we did not feel that the test was of any help to us in deciding whether or not to operate.

At the time when we were considering splenectomy in case 1 we were not aware of Moore's patient who was splenectomized successfully even though there was marrow hypoplasia. However, Dr. H. R. Peters recommended that since the spleen is not essential for life or health [18] we would probably do the patient no harm by removing it. The good result obtained in our patient, as shown by the improvement in his health and vigor and the return to normal of the blood picture, seem to indicate that even with a hypoplastic bone marrow the removal of the spleen is curative.

How does one explain the fact that our first patient and those of Moore and Williams showed a hypoplastic marrow whereas Doan and others stress the importance of a hyperplastic marrow as one of the criteria for the diagnosis of the neutropenic syndrome? It is our feeling that the cases which show a decrease in the cellularity of the bone marrow probably represent the same clinical entity in a different stage of the disease. It is possible that they may previously have had hyperplastic marrow, but owing to the prolonged duration of the disease the bone marrows became exhausted (hypoplastic) as suggested by Darling, Jackson and Parker [19] and Fitzhugh and Krumbhaar [20] in their papers on agranulocytic angina. Some evidence for this possibility is seen in our first case, in which the white cell counts averaged about 3400 and the neutrophiles about 70 per cent in 1941 and later dropped to an average of 1500 and 26 per cent, respectively, in 1946 (table 1).

We prefer to classify our patients with the primary splenic neutropenic group rather than with the primary splenic pancytopenic group because, although there were decreases in the red cells and platelets in case 1, these decreases were mild and asymptomatic, and because in case 2 there was a diminution in the granulocytes only.

In regard to the anemia in this blood dyscrasia it should be noted that Doan's cases all showed anemia which was hemolytic in type. In our case with anemia (case 1) no evidence of hemolysis could be demonstrated since the van den Bergh, icteric index and reticulocyte counts were all normal. It is probable that the anemia here was inhibitory in type, as suggested by Abrami [21] who states that splenomegalic anemia may be of two types, hemolytic or inhibitory.

Summary and Conclusions

1. Two cases of primary splenic neutropenia with arthritis (so-called Felty's syndrome) are presented.

2. Both showed clinical improvement following splenectomy with a return to normal of the leukocyte count.

3. The bone marrow in one case was hypoplastic rather than hyperplastic.

4. Splenectomy is of value even in the face of a hypoplastic bone marrow.

5. The mental outlook of the patient is brightened by the knowledge that he is better able to resist infections.

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CHRONIC HEADACHE DUE TO MASKED HYPOTHYROIDISM *

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ONE of the most baffling conditions a physician is called upon to treat is a chronic distressing headache in which a thorough physical examination, including a survey of the eyes, nose, and central nervous system, is essentially negative. Many of these patients are noticeably nervous and apprehensive yet assurance and sedation do not produce amelioration.

In the past few years I have collected a group of 20 patients with distressing headaches in which the basal metabolism was found to be below normal (table 1). With the administration of thyroid extract these patients obtained gratifying relief. In many the headaches had previously been considered psychogenic in origin, since no other demonstrable etiology could be discovered upon examination.

TABLE I

Case	Patient	Age	Weight	Headache	Sensitivity to Cold	Fatigue	Initial B.M.R.	Resting Pulse	Improvement with Thyroid
1	S. F. ♀	26	N	Severe frontal	+	+	−17	60	Marked
2	S. Z. ♀	35	U	Dull diffuse	0	+	−25	76	Marked
3	M. R. ♀	43	N	Frontal-occipital	+	+	−21	66	Marked
4	M. S. ♀	47	N	Dull vertical	0	+	−13	58	Marked
5	D. S. ♀	36	N	Throbbing occipital	+	+	−19	56	Moderate
6	C. S. ♀	38	N	Dull vertical	+	+	−26	70	Marked
7	M. S. ♀	46	N	Dull diffuse	0	+	−18	64	Marked
8	S. W. ♀	26	N	Dull diffuse	+	+	−22	56	Marked
9	E. H. ♀	32	N	Diffuse	+	+	−24	66	Marked
10	F. F. ♀	55	N	Dull frontal	+	+	−24	56	Moderate
11	C. M. ♀	39	O	Dull diffuse	0	0	−18	60	Marked
12	R. S. ♀	44	N	Severe diffuse	0	+	−17	60	Slight
13	M. S. ♀	39	O	Dull diffuse	0	0	−16	70	Marked
14	Y. T. ♀	37	U	Dull diffuse	0	+	−20	70	Moderate
15	B. Z. ♀	37	U	Dull diffuse	0	+	−12	68	Moderate
16	D. L. ♀	41	O	Dull diffuse	0	+	−21	66	Slight
17	M. D. ♀	32	N	Left occipital	0	+	−15	58	Slight
18	J. S. ♂	40	U	Vertical	0	+	−16	60	Marked
19	M. K. ♂	38	O	Diffuse	0	0	−13	56	Marked
20	S. L. ♂	50	O	Dull diffuse	0	+	−14	58	Moderate

N denotes normal weight, U underweight, and O overweight.

The headache in these patients was usually constant throughout most of the day and often persisted for weeks at a time. It was accentuated by undue physical strain or excitement and relieved by rest. The headache was char-

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acteristically bilateral in its distribution and sometimes localized to either the occipital, the vertical, or the frontal area. In other patients its distribution was vague. The cephalalgia varied in intensity from a dull annoying distress to a severe throbbing ache. It differed quite distinctly from typical migraine in that the headache was not periodic, unilateral, nor accompanied by nausea and vomiting. It is interesting to note that two of the patients (cases 13 and 15) suffered in addition from attacks of typical migraine, but they did not obtain any relief from the seizures of hemicrania while under thyroid therapy.

Aside from some vague clinical suggestions, there were no pronounced stigmata obtained in history or physical examination to indicate hypothyroidism in this group. Only one of the entire series exhibited moderate myxedema with obvious clinical evidence of hypothyroidism. The remaining patients did not appear sluggish and, on the contrary, many were quite apprehensive and alert. Seventeen of the 20 remarked that they became easily exhausted especially towards evening. Seven of the 20 complained of unusual sensitivity to cold upon exposure. Some did remark on the lack of appreciable perspiration in hot weather. None showed any unusual dryness or puffiness of the skin. Some patients commented on some depletion of hair from the scalp, but in none was any thinning of the eyebrows detected. There was no unusual distribution of fat, and only five of the group were slightly or moderately obese, 11 being normal in weight and the remaining four underweight.

The series was composed predominantly of females, 17 of the 20, and their ages ranged from 26 to 55 years. Their basal metabolic rates varied between — 12 per cent to — 26 per cent. The one patient exhibiting clinical myxedema registered the lowest rate. Blood cholesterol values were obtained in only two of the patients and were normal.

Desiccated thyroid extract in daily doses of 1 to 3 grains brought about considerable amelioration of the headaches in 17 of these patients, usually after a latent period of 10 to 14 days, and the basal metabolic rate gradually rose to normal. Many felt as though a weight had been removed from their heads and they expressed surprise at their greater energy. It was found best to start therapy with a smaller dose, 1 grain daily, since these patients were found to be sensitive to thyroid and larger initial doses occasionally produced palpitation and irritability. Three patients obtained only slight relief from the headaches, but of these, two also suffered from hypertension (cases 12 and 16). The remaining 18 patients all had a blood pressure usually within the range of low normal. A moderate secondary anemia, observed in only two patients, did not respond to iron therapy alone, but did improve on combined iron and thyroid medication.

This group of patients is part of a larger series of 44 patients with mild hypothyroidism and low basal metabolic rates, who were all observed during the same period. The remaining patients did not experience any headaches

but did complain of asthenia, lethargy, intolerance to cold, or excessive loss of hair from the scalp, and they also manifested improvement with thyroid medication.

As defined by Werner,[1] hypothyroidism is a condition in which the thyroid gland fails to supply sufficient internal secretion to the tissues of the body to maintain chemical activity at a normal level. It seems that the headaches of which these patients complained resulted from the additional stress and strain under which they were laboring because of a deficiency in circulating thyroid hormone. Their response to thyroid therapy tends to confirm this view, especially since previous treatment with aspirin or sedatives was ineffective.

Means[2] has noted that some perfectly healthy individuals may record a low metabolic rate and terms this hypometabolism without any clinical significance. This is illustrated by several other patients who exhibited a low basal metabolic rate as an isolated finding and who did not require thyroid, nor were they helped if given the drug. These patients felt entirely well or presented symptoms unrelated to hypothyroidism. However, the patients presented in this report are undoubtedly true cases of hypothyroidism which are milder than those seen with the features of myxedema. As a matter of fact, most of the patients that I have seen with pronounced clinical manifestations of myxedema are too dull and apathetic to complain of headache.

That chronic persistent headache is common in mild hypothyroidism has been recorded previously by other observers. Higgins[3] in 1925 noted that some of his cases of mild hypothyroidism complained of headache and fatigue. Seward[4] in 1935 observed 53 patients with the mild type of hypothyroidism in which 18 suffered from headaches either at the vertex or in the suboccipital area. Schultz[5] in 1936 reported a group which she termed non-myxedematous hypothyroidism and emphasized neurasthenia and generalized headaches as conspicuous clinical features. Harstock[6] in 1939 presented a large group of patients which he classified as incipient hypothyroidism. He remarked that 75 per cent of these patients would be overlooked, if one expected to find some of the typical features of myxedema for the diagnosis. Many of his patients complained of chronic headache which he[6] attributed to their general fatigue and hypotension. Werner[1] in 1942 also noted that some of his patients with mild hypothyroidism suffered from aching in the occipitocervical region with radiation to the shoulders and interscapular area.

To be sure, hypothyroidism is not a frequent cause of headache among the various patients with this complaint seen in practice. Nevertheless this type is remarkable because of its chronicity, its annoying disability, and its favorable response to thyroid therapy.

The following four illustrative cases are briefly presented.

Case Reports

Case 1. Mrs. S. F., aged 26, was first seen in March 1937 complaining of almost continuous bilateral frontal headaches increasing in severity toward evening. She felt very irritable and readily became exhausted, finding it difficult to do her housework. She experienced chilliness on exposure to cold and preferred warm weather. Physical examination revealed a tall alert young woman of normal weight, with a blood pressure of 120 mm. Hg systolic and 80 mm. diastolic, and a pulse rate of 60. Otherwise examination was essentially normal, the blood Wassermann reaction was negative, and the urine normal. Sedatives and aspirin were prescribed without any relief. A change of glasses recommended by an ophthalmologist, and several nasal drainages for suspected sinusitis did not alleviate the headaches. In July 1937, a basal metabolism test recorded a rate of — 17 per cent, and desiccated thyroid 2 grains daily was prescribed. Within two weeks the headaches had entirely disappeared and the patient felt as though rejuvenated. She continued to take thyroid, averaging 1 to 2 grains daily, almost continuously for nine years, during which time she bore two children. When she stopped taking the drug for over a month, the headaches and tiredness returned. In January 1944 her basal metabolic rate was — 12 per cent while on 1 grain of thyroid daily. At no time did she demonstrate any clinical signs suggestive of myxedema.

Case 2. Miss S. Z., aged 35, was seen in December 1944 with complaints of extreme weakness, nervousness, chronic fatigue, and a constant ache vaguely distributed over the entire head. The headache would often become much more severe at night and would then localize at either temple. Examination disclosed an active woman with bright prominent eyes of the familial type. She was considerably underweight, her blood pressure was 138 mm. Hg systolic and 90 mm. diastolic, and her pulse rate was 76. Despite a high caloric diet and sedatives, her headaches continued, and she was unable to gain weight. In April 1945, a basal metabolism test revealed a surprisingly low rate of — 25 per cent, while her resting pulse rate was 74. Blood cholesterol was 210 mg. per cent. On 1 grain of thyroid daily there was a slight improvement and when the dose was doubled, she became completely relieved of her headaches, gained some weight, and felt much more energetic. In May 1945, she stopped the thyroid medication for six weeks and experienced a return of headaches and lethargy. In March 1946 her basal metabolic rate was — 10 per cent while on 10 grains of thyroid per week.

Case 8. Mrs. S. W., aged 26, was seen in June 1943 because of weakness, dizziness, and frequent headaches. The headaches recurred regularly every afternoon, were diffuse in distribution, and were associated with subjective dizziness. Aside from some evident pallor, nothing remarkable was found upon examination. Her blood pressure was 110 mm. Hg systolic and 80 mm. diastolic, and her weight was normal. A blood study revealed a hemoglobin 64 per cent Sahli, red blood cells 3,100,000, and white blood cells 6,200 of which 45 per cent were neutrophiles, 43 per cent lymphocytes, 7 per cent monocytes, and 5 per cent eosinophiles. Blood cholesterol was 240 mg. per cent. A stool examination was negative for parasites. Despite large doses of iron, the hemoglobin remained stationary and the symptoms persisted. She also remarked that she felt quite sensitive to cold. In October 1943 a basal metabolic rate of — 22 per cent was recorded, while the resting pulse rate was 56. Desiccated thyroid 1 grain daily was prescribed and the iron medication continued with some improvement. In December the daily dose of thyroid was increased to 2 grains, and she experienced a complete remission in that she no longer suffered headaches nor dizziness and had gained some weight and strength. Her hemoglobin rose to 80 per cent. In October 1946 her basal metabolic rate was — 9 per cent, while on 2 grains of thyroid daily.

Case 18. Mr. J. S., aged 40, visited me in March 1946 with diversified complaints of asthenia, dizziness, dull precordial distress, and generalized muscular aches. A diagnosis of neurocirculatory asthenia was made, and he improved with sedatives and psychotherapy. In June 1946 his symptoms recurred together with a continuous distressing headache centered particularly on the top of his head. Examination revealed nothing of note, his weight was slightly below normal, and his blood pressure was 108 mm. Hg systolic and 70 mm. diastolic. A basal metabolic rate of — 16 per cent was obtained, and desiccated thyroid 1 grain daily was prescribed. After nine days, the headaches disappeared and there was a considerable improvement in his neurasthenic symptoms. In September, while on thyroid therapy, he felt much stronger than he had felt for years and experienced no headaches.

Summary

A bilateral headache, remaining for weeks, may be due to mild hypothyroidism which is not readily recognized by physical examination.

Suggestive features of such masked hypothyroidism are asthenia, sensitivity to cold, slow resting pulse rate, and a moderate hypotension.

The basal metabolic rate should be determined in any patient complaining of persistent headaches, in whom no cause is discernible upon routine history and physical examination.

This type of headache is remarkable for its favorable response to thyroid medication.

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RENAL GLYCOSURIA: A REVIEW OF THE LITERATURE AND REPORT OF FOUR CASES *

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IN the evaluation of the meliturias, renal glycosuria is usually considered a rare clinical entity. However, some recent studies refute this impression or at least bring its validity into question. The condition is benign and carries a good prognosis. The likelihood of its being accorded serious import or even being treated as diabetes mellitus, gives renal glycosuria a prominent place in the diagnostic consideration of the medical work-up of any case of melituria. The reports of Blotner and Hyde [1] and the Peels [2] regard renal glycosuria as a relatively common finding, the former reporting one person in 11 with melituria as having the disorder. The rigid diagnostic criteria of Marble,[3] however, were apparently not closely followed. Joslin [3] and his associates in a review of 18,000 cases of melituria report 53 cases of renal glycosuria per se and nine cases of renal glycosuria of pregnancy. Wilder [4] has reported 82 cases from the Mayo Clinic and Fowler [5] noted seven cases of renal glycosuria in 4,000 cases of melituria at the Montreal General Hospital. The highest incidence was seen in the report of the Peels [2] with 30 cases of renal glycosuria in only 115 recruits manifesting melituria. It is interesting to note that the two reports with the highest incidence of the condition occurred in series conducted on recruits who were predominantly of the younger age group.

Marble,[3] who is of the opinion that renal glycosuria is a rare condition, has set the following criteria for the diagnosis. In view of the importance of absolute diagnosis, these standards should be fulfilled prior to making the diagnosis.

1. Fasting blood sugar within normal limits and a normal glucose tolerance curve.
2. Glucose should be present in appreciable quantity in all urine specimens, whether voided in the fasting state or post-prandially. The quantity of sugar in the urine should be for the most part independent of the diet.
3. Carbohydrate utilization should be normal as evidenced by the respiratory quotient and serum inorganic phosphate after glucose ingestion.
4. Fat metabolism should be normal, ketosis being more likely to develop when the patient fasts than when he overeats.
5. Moderate doses of insulin should have little or no effect on the glycosuria.

The Station Hospital, Camp Hood, Texas, admitted 5,740 patients from May 31, 1946 to February 28, 1947, four of whom had renal glycosuria.

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The diagnosis in these patients conformed to the requisites as presented by Marble. The hospital receives military personnel and their dependents and veterans of all age groups.

Case Reports

Case 1. A 30 year old white male was admitted to the hospital June 19, 1946, with complaint of dysuria, frequency and nocturia of four months' duration. His past medical history disclosed that he had had an episode of hematuria in the spring of 1943. He was in England at the time and was hospitalized in an Army General Hospital for three months. He was cystoscoped and informed that he had "irritation of the bladder." He was hospitalized on two more occasions, once overseas and once in a zone of the interior general hospital. The patient had six cystoscopic examinations in all. He was asymptomatic from November 1945 to March 1946. His family history revealed no pertinent familial or environmental factors. No members of his family have been known to have diabetes mellitus. He had had gonorrheal urethritis in 1941 and in 1946, being treated with sulfadiazine and penicillin respectively.

The patient was 64 inches in height and weighed 132 pounds. The blood pressure was 126 mm. Hg systolic and 80 mm. diastolic. The physical examination presented no gross abnormalities other than prostatic tenderness, though the gland was not enlarged and was of normal consistency.

The blood count revealed 4,170,000 erythrocytes; 14.5 gm. hemoglobin; and 7,250 leukocytes with a normal distribution. The sedimentation rate (Wintrobe) was 1 mm. per hour. The urinalysis disclosed a 1 plus sugar test using Benedict's qualitative solution, the color being green after 5 minutes' boiling. There were 8 to 10 leukocytes per high power field (centrifuged). The Kahn reaction was negative. A fasting blood sugar determination (Folin-Wu) revealed a finding of 92.6 mg. per cent and the fasting urine specimen showed a 2 plus reduction. Further blood chemical studies of total protein and albumin-globulin ratio, non-protein nitrogen, plasma cholesterol and serum phosphorus were within normal limits. An intravenous pyelogram and chest roentgen-ray presented no abnormalities. The urinary sugar was identified as glucose using as criteria the positive reduction test and the formation of typical glucosazone crystals with phenylhydrazine.

A glucose tolerance test was done using venous blood. The Folin-Wu method was used; simultaneous phosphorus determinations were made; 1.75 grams of glucose per kilogram of body weight were given orally after 12 hours fasting. The figures below demonstrate the result of this test, disclosing a normal tolerance to glucose. The fall in phosphorus values proves adequate absorption of the glucose.

Glucose Tolerance Test

	Blood Sugar	Phosphorus	Urine Sugar
Fasting	86.4 mg. %	5.8 mg. %	Trace
½ hr.	141.6 mg. %	3.6 mg. %	4 plus
1 hr.	136.4 mg. %	2.6 mg. %	3 plus
2 hr.	96.0 mg. %	3.0 mg. %	3 plus
3 hr.	78.4 mg. %	3.2 mg. %	1 plus

Urine specimens were collected every hour on the hour for 24 hours and each specimen manifested quantities of sugar varying from a trace to 2 plus. The quantitative determination of the 24 hour specimen for sugar was 0.64 gram per cent. The patient in a fasting state received 15 units of crystalline insulin subcutaneously which

did not affect the glycosuria. He was never found to be without glycosuria. A diet containing 400 grams of carbohydrate, 130 grams protein and 100 grams of fat was given the patient for three days. His subsequent urine specimens and those of the third day of his diet continued to show persistent glycosuria with no appreciable change in the amount of sugar. There was likewise no change in urinary sugar on a diet of carbohydrate 100 gm., protein 60 gm. and fat 60 gm.

This patient had been treated on two occasions for diabetes mellitus using both insulin and dietotherapy. There were multiple cystoscopic examinations made which may or may not have been necessary. At any rate, this patient's melituria had not received adequate study to establish its type and warrant a conclusion regarding disposition of the man. He came to the hospital for Certificate of Disability Discharge on the basis of diabetes mellitus and has since returned to duty and has been asymptomatic for six months.

Case 2. A 21 year old white male was admitted to the hospital January 8, 1947, for tonsillectomy. He was a tall asthenic individual with a history of severe recurrent tonsillitis of 18 months' duration and complaints of easy fatigability and a mild progressive asthenia of about six months' duration. The finding of a 1 plus melituria and a 1 plus albuminuria had never occurred before to the patient's knowledge. His last urinalysis was May 7, 1944. He had done considerable duty in the South Pacific. He stated that there was "lots of kidney trouble" in his family. He has one brother who has diabetes mellitus.

The tonsils were embedded and cryptic. There was a cardiac arrhythmia exaggerated by exercise and rapid respiration which was interpreted as multiple auricular premature contractions with an associated sinus arrhythmia.

The urine continued to manifest a 1 plus albuminuria and varying degrees of melituria. The blood count was normal; blood chemistry determinations were normal for serum cholesterol, blood urea, phosphorus and sugar; Kahn test was negative. Three basal metabolic rates were within normal limits. A urea clearance test of renal function was normal. The chest roentgen-ray disclosed no abnormalities. The patient's electrocardiogram demonstrated multifocal auricular and ventricular premature contractions with occasional atrio-ventricular dissociation. Sinus arrhythmia was present in marked degree. The tracing was otherwise normal. His glucose tolerance test, using the method above described, demonstrated a normal tolerance for glucose. Both arterial and venous blood sugars were done to note the arteriovenous difference and determine whether or not adequate utilization was occurring in the tissues. Serum phosphorus determinations were made simultaneously to study glucose absorption. (The capillary micro-method of Folin-Wu was used to determine the arterial blood sugars.)

Glucose Tolerance Test

	Blood Sugar		Phosphorus	Urine Sugar
	Arterial	Venous		
Fasting	91.7 mg. %	82.6 mg. %	5.5 mg. %	1 plus
½ hr.	208.3 mg. %	163.9 mg. %	3.8 mg. %	2 plus
1 hr.	256.4 mg. %	178.6 mg. %	3.8 mg. %	4 plus
2 hr.	210.5 mg. %	151.5 mg. %	3.6 mg. %	4 plus
3 hr.	121.2 mg. %	71.7 mg. %	4.0 mg. %	4 plus

The urinary sugar was identified as glucose. Hourly urine specimens collected around the clock all contained glucose in varying significant quantities and the quantitative determination on the 24 hour specimen disclosed 0.6 gm. per cent glucose. There was no change in the glycosuria with either a high or low carbohydrate diet. The administration of insulin did not alter the glycosuria. All specimens of urine manifested a 1 plus to 2 plus albuminuria with from 10 to 20 leukocytes in a centrifuged specimen. No erythrocytes were seen.

The study of this patient suggests that his renal glycosuria had its onset some time between 1944 and 1947. The history of severe, recurrent tonsillitis also suggests a streptococcal origin of widespread vascular disease with, perhaps, an allergic-hyperergic response on the part of the heart and the kidneys. This idea is based on the conception of the rheumatic syndrome as advanced by Coburn. It is conceivable that enough vascular damage could have occurred to the blood supply of the renal tubules to alter the reabsorption gradient of glucose by disrupting the enzyme system concerned with its reabsorption from the tubules. The phosphorylation mechanism of glucose reabsorption from the tubules has been postulated.

Case 3. A 28 year old white male was admitted to the hospital on February 18, 1947, for a nasal sub-mucus resection and rhinoplasty. His history was that of severe frontal and occipital headaches and chronic cough productive of thick, gray, nummular sputum. He stated that he had had a "constant cold" for six years. The patient had had scarlet fever as a child and a tonsillectomy at the age of 13 years. The family history was negative. He smoked about one and a half packages of cigarettes a day. There were offered complaints of urinary frequency and nocturia, three or four times nightly; ease of fatigue; night sweats; "nervousness," apprehension and anorexia. His physical examination revealed a markedly deviated nasal septum and a thick turgescent nasal mucosa. His blood pressure was 122/76.

The Mantoux test was 1 plus. His blood chemistry studies, including blood urea, fasting blood sugar and cholesterol, were normal. The blood count was normal except for a leukocytosis of 13,000 cells with 82 per cent predominance of polymorphonuclear cells. Paranasal sinus and chest roentgen-rays were normal as was the electrocardiogram. The urinalysis was normal except for a 2 plus melituria. The sugar was identified as glucose. A blood urea clearance test was within normal limits. The glucose tolerance test using arterial and venous sugar determinations plus simultaneous phosphorus studies is shown below.

Glucose Tolerance Test

	Blood Sugar		Phosphorus	Urine Sugar
	Arterial	Venous		
Fasting	92.0 mg. %	72.2 mg. %	5.7 mg. %	Neg.
½ hr.	177.0 mg. %	127.4 mg. %	3.4 mg. %	2 plus
1 hr.	114.3 mg. %	86.6 mg. %	2.8 mg. %	3 plus
2 hr.	97.3 mg. %	81.6 mg. %	2.4 mg. %	1 plus
3 hr.	57.2 mg. %	46.0 mg. %	3.6 mg. %	1 plus

This test demonstrates normal glucose absorption and tissue utilization. This patient, in contradistinction to the others, had negative urine sugar tests from about midnight until after breakfast the next morning. All other urine specimens obtained

hourly contained quantities of glucose varying from a trace to 3 plus. The quantitative glucose determination on the 24 hour specimen was 0.64 gm. per cent glucose. The urinary glucose was not affected by a high or low carbohydrate diet as described in case 1. Crystalline insulin in a dosage of 15 units subcutaneously was given in the fasting state and the glycosuria remained unchanged as determined in hourly urine specimens collected for six hours.

This case does not completely satisfy the rigid criteria of Marble in that the patient was aglycosuric from midnight until 7 a.m. However, all other types of melituria were excluded and it was felt that the diagnosis could be tentatively made. It may be noted that low values for sugar were obtained in the last specimens of the glucose tolerance test. There were no hypoglycemic symptoms noted and it was thought that these low values may be attributed to the method of determination used. It is now recognized that the Folin-Wu method gives results which are too low for low values and too high for high values. Cantarow and Trumper [6] note that "the Benedict's 1928 and 1931 reagents which may be used with the Folin-Wu tungstic-acid filtrate, are relatively unaffected by glutathione and other saccharoids. The use of the Benedict's reagent lessens the possibility of errors of interpretation due to this inaccuracy of method."

Case 4. A 26 year old white soldier was admitted to the hospital February 20, 1947, for hemorrhoidectomy. This patient was first told that he had sugar in his urine in 1937 and was treated for diabetes mellitus for several months by dietotherapy but received no insulin. He had stopped treatment of his own accord. The patient has one brother who has diabetes and is treated with both diet and insulin. One sister has melituria but has never been treated. A paternal uncle has diabetes mellitus requiring both insulin and diet for its control. The patient's mother has hypertensive cardiovascular disease. The remainder of the history and systemic review were negative. The physical examination was negative except for pharyngeal adenopathy and large external hemorrhoids.

The blood count was normal and the urinalysis disclosed a 3 plus melituria. Blood chemical tests, including the blood urea, fasting blood sugar and cholesterol determinations, were normal. A blood urea clearance test of renal function was within normal limits. The chest roentgen-ray and electrocardiogram showed no abnormalities. The glucose tolerance test is shown below. This test demonstrates normal glucose absorption and tissue utilization. It also suggests an increased tolerance to glucose which in turn suggests either a decreased rate of hepatic glycogenolysis or increased tissue glycogenesis and glycolysis.

Glucose Tolerance Test

	Blood Sugar		Phosphorus	Urine Sugar
	Arterial	Venous		
Fasting	84.4 mg. %	81.0 mg. %	3.88 mg. %	3 plus
½ hr.	117.5 mg. %	101.5 mg. %	3.84 mg. %	4 plus
1 hr.	85.8 mg. %	71.7 mg. %	3.07 mg. %	4 plus
2 hr.	86.9 mg. %	62.3 mg. %	3.06 mg. %	3 plus
3 hr.	70.2 mg. %	53.3 mg. %	3.20 mg. %	3 plus

The urinary sugar was identified as glucose. Hourly sugar determinations on the urine were made for 24 hours and each specimen contained 2 plus to 4 plus sugar. Only two of these specimens were 2 plus, 12 were 4 plus and 10 were 3 plus. The quantitative determination for sugar on the 24 hour specimen was 0.77 gram per cent of glucose. Crystalline insulin was given subcutaneously as described above and the glycosuria was unaffected. There was noted no change in the glycosuria when the patient was placed on both high and low carbohydrate diet as described in the first case.

The family history in this case was interesting in that there are apparently two true diabetics in the family and one person with melituria of undetermined type. The familial incidence of renal glycosuria has been pointed out by Brown and Poleshuck.[7] It is not known whether members of the patient's family represent cases of true diabetes or renal glycosuria. Blotner and Hyde report a family history of diabetes in 32 per cent of 22 patients with renal glycosuria.

This patient also has been treated for diabetes mellitus though only for a short time. Thoroughgoing study of such individuals is certainly indicated in that they frequently offer difficult problems and are apparently frequently mistaken for true diabetes. According to present knowledge renal glycosuria is an innocuous disorder and hence correct diagnosis is of considerable importance to the patient.

Comment

Renal glycosuria is a condition which is considered by most authorities to be rare. However, Blotner and Hyde and the Peels report a rather high incidence by comparison with other authors. At any rate it seems likely that many people with melituria of some type are being needlessly treated for diabetes mellitus. There is little doubt that real damage may be done by such therapy. If such a patient is losing sugar steadily in his urine, it would seem only sensible that a liberal carbohydrate diet is indicated. Certainly insulin administration can be of no value in the treatment of renal glycosuria and may well do considerable harm. These patients frequently complain of ease of fatigue and malaise which symptoms may well have their origin in a low carbohydrate intake. Marble recommends prolonged observation in these patients because of the strong family history of diabetes. Renal glycosuria and diabetes mellitus are two separate entities and the consensus is that the former does not progress to diabetes. True idiopathic renal glycosuria is regarded as a permanent condition which is in most instances asymptomatic or only mildly so.

Renal glycosuria is characterized by a low renal threshold for sugar. It is well established that the urinary sugar is present because of incomplete reabsorption of sugar by the proximal convoluted tubules of the kidneys. The reason for this abnormality is not well understood. All of the cases reported here have low renal thresholds as proved by the presence of glycosuria with a normal or subnormal level of blood sugar. It has been postu-

lated that a deficiency of tissue phosphatase may be the abnormality producing consequent interference with the phosphorylation mechanism in the renal tubules on which sugar reabsorption depends. Another possible etiology is that suggested by Thomas and Southward who conjecture that the renal threshold is under hormone control. Comparison is made with diabetes insipidus in which the hormone of the posterior pituitary exerts its well known effect on the renal tubules. The renal glycosuria of pregnancy fits this conception in that there exists in pregnancy a hormonal imbalance. The second case in this group apparently developed his renal glycosuria following a series of streptococcal infections. The thought that this may be more than coincidental is offered. The widespread vascular lesions apparently produced by repeated hemolytic streptococcal infections may well produce changes in the blood supply to the renal tubules which in turn could alter the tubular physiological function. There is no experimental evidence that has come to the author's attention to support this conjecture. Brush [9] reports renal glycosuria as a "complication of advancing age, and is found particularly in individuals who have had some type of obstructive uropathy." He states that "experimental work has proved that functional changes in the kidneys may preëxist macroscopic and microscopic evidence of altered structure." He postulates that these functional changes may be due to extra-renal influences such as degenerative disease of the cardiovascular system or organs or to intra-renal disturbances.

The treatment of renal glycosuria is simple. A liberal and varied diet should be given with perhaps some emphasis on carbohydrate intake. The patient should be advised that his condition is benign and reassured that his prognosis is good. Certainly insulin is not indicated. If the diagnosis of diabetes mellitus is suspected but not proved, there is no indication for haste in instituting therapy. Naunyn's principle of determining the carbohydrate balance by giving a measured diet and estimating the loss of glucose in the urine daily seems worthy of mention. Insulin used in a patient with depleted hepatic glycogen stores may produce acetonemia and acetonuria. Somogyi [10] has shown that a low carbohydrate intake and ill-advised use of insulin may produce increased hepatic glycogenolysis with each episode of hypoglycemia, thus leading to increased hepatic fat and protein metabolism. There occurs consequent increase in ketone production. A clinical ketonuria may thus be induced in the absence of glycosuria. Insulin in such an instance is clearly contraindicated.

Summary

1. The literature of renal glycosuria is reviewed and four cases of the disorder are reported. The diagnostic criteria of Marble are used in making the diagnosis.

2. Emphasis is placed on the importance of thoroughgoing study of any case of melituria and the difficulties encountered in discriminating renal glycosuria from diabetes are considered.

3. The study included determinations of both arterial and venous blood sugars in the glucose tolerance tests in order to prove adequate removal of glucose by the tissues from the arterial blood. Serum phosphorus determinations were simultaneously made to study the absorption of the glucose and the phosphorylation mechanism.

4. All cases occurred in military personnel which adds to the importance of accurate diagnosis and consequent disposition of these patients from army hospitals.

5. The dangers of treating renal glycosuria as diabetes are reviewed.

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DIFFERENTIAL DIAGNOSIS BETWEEN MEDICAL AND SURGICAL JAUNDICE BY LABORATORY TESTS *

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DESPITE the great strides of laboratory medicine in the past two decades and the subsequent elaboration of many liver function tests, the jaundiced patient still presents today a challenging diagnostic problem. There is little difficulty in recognizing the hemolytic variety of jaundice (retention type) primarily by the absence of bile from the urine, the low or absent direct serum bilirubin and evidence of hemolysis. However, to differentiate the two types of regurgitation jaundice, the medical (due to acute or chronic hepatitis or to cirrhosis) from the surgical (due to stones, tumors or strictures), is often difficult. Even the experienced clinician concedes a relatively high number of diagnostic failures as evidenced by superfluous as well as by delayed operations. The hope of improving this unsatisfactory situation by developing new liver function tests has to date only partly materialized.

The performance of a number of different liver function tests was therefore recommended—a "composite" study of liver function.[1] This created a problem of how to dovetail the results of the different tests into a unified diagnostic approach. Among several presented attempts,[2, 3, 4, 5, 6, 7, 8] the profile derived from graphic recording of the results of liver function tests in a given case as described by Watson and Hoffbauer [1] appeared promising.[9] Nevertheless, to date, profiles characteristic of individual conditions are not as yet available. Moreover, profound knowledge of the physiologic basis is needed for the interpretation of the "composite" study of liver function.

Another approach to be presented below is to trace the thought processes which lead to a diagnosis in a jaundiced patient, and to analyze the rôle which the results of liver function tests play in them. To simplify this otherwise unwieldy problem, the approach was limited to the differentiation between medical and surgical jaundice. Only the initial series of liver function tests was taken into consideration and thus the duration of jaundice was not taken into account. Experiences with a group of 285 jaundiced patients served as the basis for this attempt.

This analysis had a twofold purpose: first, to develop a graphic scheme which may facilitate the recognition of the diagnostic problems in jaundice, and secondly, to evaluate empirically which liver function tests in use, with-

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out reference to their physiologic basis, were, from a practical standpoint most helpful in determining the diagnosis.

Material and Method

The material studied consisted of 285 cases of various types of jaundice excluding the hemolytic variety. It included only cases in whom the diagnosis was definitely established by the follow-up course, subsequent biopsy, operation and/or necropsy findings. The patients were observed in a large general charity hospital. This is reflected by the distribution of the various types (table 1). Cirrhosis was relatively common. Acute hepatitis as well as obstructive jaundice was usually seen in somewhat advanced stages.

Table I

Final Diagnoses in 285 Analyzed Cases of Jaundice

Acute Hepatitis	Cirrhosis	Benign Obstruction	Malignant Obstruction
83	122	44	36

The examined cases fell into two groups: Group I consisted of 125 cases studied between 1941 and 1943, while Group II comprised 160 cases, studied during 1946 and 1947. In the first group, the following determinations were performed: (*a*) total serum protein; (*b*) albumin-globulin ratio; (*c*) serum non-protein nitrogen; (*d*) cephalin-cholesterol flocculation [10]; (*e*) total serum cholesterol; (*f*) cholesterol ester/cholesterol ratio [11]; (*g*) serum alkaline phosphatase [12]; (*h*) hippuric acid synthesis after oral administration [13]; (*i*) urinary urobilinogen in a 24 hour specimen [14]; (*j*) concentration of fecal urobilinogen [15]; (*k*) plasma vitamin A [16]; (*l*) bromsulfalein retention 45 minutes after administration of 5 mg. per kg. body weight (in cases with only slight jaundice); and (*m*) total serum bilirubin.

In the second group, the same tests were performed with the following exceptions: the thymol turbidity was determined in all instances.[17, 18, 19] The hippuric acid synthesis after intravenous administration [20] (replacing the oral method) and the plasma vitamin A determinations were done only in selected cases; moreover, in the majority of these patients the urinary urobilinogen was determined as units in a two hour afternoon specimen.[21]

These examinations were supplemented with the usual clinical observation, additional laboratory studies, biopsy findings, and in some instances with the findings at operation or necropsy.

The final diagnosis was obviously not made in all cases after the primary workup because the analytical thought processes described below were not correctly applied. A number of diagnostic failures—not quite 5 per cent—occurred, many of which might have been avoided according to retrospective analysis.

The described thought processes will be composed of a number of steps. In the description of each step, two points will be made: (1) analysis of the

function tests which are taken into consideration in making this step, and (2) discussion of the cases in which this step was not justified.

Diagnostic Route

The first problem in the differential diagnosis of the jaundiced patient is the distinction between presence or absence of liver cell damage and of marked interference with the bile flow. Some interference with the bile flow is found in every patient with regurgitation jaundice. There are gradual transitions from slight interference to complete exclusion of bile from the duodenum, as is typically seen in complete extrahepatic mechanical biliary obstruction. Therefore, arbitrarily the term "marked interference with the bile flow," as used hereafter, has been defined by the results of function tests as characteristically found in established extrahepatic biliary obstruction. On this basis, in general, the patient with medical jaundice has liver cell function impairment; the patient with surgical jaundice marked interference with the bile flow.

The liver function tests used can be divided into two groups: (*a*) those

Table II

Pathologic Levels Chosen in Liver Function Tests Which Are Grouped as to Their Significance

Tests Indicating			
Liver Cell Damage		Marked Bile Flow Interference	
Test	Pathologic Level	Test	Pathologic Level
Cephalin cholesterol flocculation	Above 2+	Urinary urobilinogen reduced	Less than 1.0 mg. 24 hrs. or less than 0.5 U in 2 hrs.
Thymol turbidity	Above 4 U	Fecal urobilinogen reduced	Less than 10 mg. %
Albumin-globulin ratio	Below 1.25	Serum alkaline phosphatase	Above 15 Bodansky units
Cholesterol ester/cholesterol ratio	Below 50%	Serum total cholesterol	Above 300 mg. %
Urinary urobilinogen (elevated)	Above 3 mg./24 hrs. or above 3 U in 2 hrs.		
Hippuric acid Oral test Intravenous test	 Below 3 gm. Below 0.7 gm.		
Non-protein nitrogen	Above 40 mg.%		
Plasma vitamin A	Below 15 micrograms		
Bromsulfalein	Above 6% retention in 45 min. after injection of 5 mg./kg.		

which indicate liver cell damage; and (*b*) those which indicate marked impairment of bile flow (table 2).

The classification in table 2 agrees to some extent with that recently presented by Watson and Hoffbauer [1] in which the tests are divided as indicating hepatocellular or cholangiolar dysfunction. Regurgitation jaundice appears to be a cholangiolar disturbance resulting in back flow of bile through the smallest bile ducts. The previously held view that dissociation of the liver cell cords is responsible has been given up since the latter is usually a postmortem phenomenon.[22] Total serum bilirubin is elevated and bilirubinuria is present in every regurgitation jaundice. Though, therefore, hyperbilirubinemia and bilirubinuria appear to be due to cholangiolar dysfunction they are found in both types—in medical and surgical jaundice—and obviously from the practical standpoint are not characteristic for either group.

A decrease of prothrombin may be due to both exclusion of bile from the duodenum and liver cell damage. The prothrombin test was therefore omitted from table 2. Bromsulfalein retention may be due to both liver cell damage and marked bile flow interference. However in the presence of a mild degree of jaundice (the only time it was utilized in this series) bromsulfalein retention was only due to the former. The level of total cholesterol chosen is higher than the usually accepted pathologic borderline. However, only the high levels indicate marked bile flow interference since levels up to 300 mg. per cent are not infrequently found in other conditions. The occasional reduction of total cholesterol in hepatitis was not taken into consideration. A level of serum alkaline phosphatase between 4 and 15 Bodansky units is definitely pathologic in the adult. Such an elevation is very commonly found in all types of medical jaundice [28] and therefore can hardly serve as a differential diagnostic criterion between surgical and medical jaundice. Levels above 15 units have been selected since they are commonly seen in conditions in which a mechanical interference with the bile flow can be demonstrated. Since the cause of the elevation of the alkaline phosphatase level in jaundice is as yet not established, it is questionable whether the levels between 4 and 15 units represent lesser degrees of bile flow interference or liver cell damage. In contrast to the older concept that the elevation is due only to reduced excretion of alkaline phosphatase in the bile, increased formation in overstimulated pathologic liver cells has also been claimed to be responsible.[24, 25, 26, 27]

It is generally accepted that almost every one of the mentioned tests for liver cell damage may yield false positive results. It was, therefore, felt advisable to start under the assumption that liver cell damage is present in a jaundiced patient only if at least two of the given tests were positive. For the establishment of marked impairment of the bile flow in the presence of jaundice, one positive test was considered necessary. The correctness of these assumptions were attested by the results mentioned below.

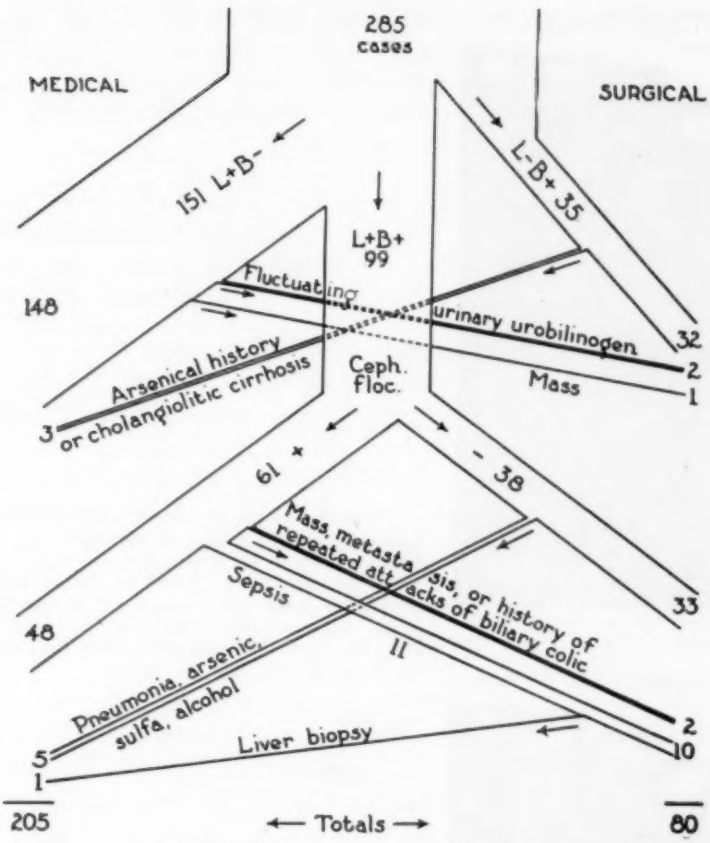

FIG. 1. Diagram demonstrating the route of the thought processes in the differential diagnosis between medical and surgical jaundice based primarily on laboratory examination. The width of the individual lanes indicates the number of cases in each. "L" indicates tests for liver cell damage; "B" tests for marked interference with bile flow.

On this basis, the cases studied were initially divided into three groups (figure 1):

(*a*) Those having liver cell damage without marked bile flow interference (L + B —) (151 cases).
(*b*) Those having marked interference with bile flow but no liver cell damage (L — B +) (34 cases).
(*c*) Those having both (L + B +) (98 cases).

A. Cases with Liver Function Impairment but without Interference with Bile Flow. A priori the cases of this group were considered as medical jaundice.

1. Analysis of tests.

A variable number of the function tests indicating liver cell damage was positive in each individual case. Four cases in which only one test was

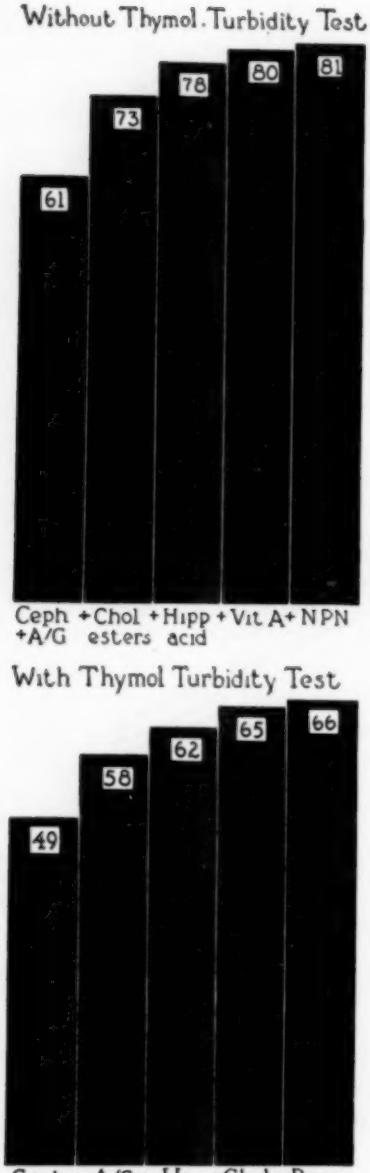

FIG. 2. Columns demonstrating the number of cases in which liver cell damage was correctly diagnosed by at least two of the listed tests. They show the increase produced by taking into account additional tests. The cases of the period 1941–1943 (without thymol turbidity test) are separated from those of 1946 and 1947 (with thymol turbidity test).

positive had to be included on the basis of the clinical picture. In the overwhelming majority, however, two or more tests revealed pathologic results. Most commonly three tests were positive, rarely five or six, but never more. It seems, therefore, that in the presence of jaundice one pathologic liver function test may occasionally indicate liver cell damage, but that in general, pathologic results in at least two tests should be required to indicate it.

It is not easy to decide which combination of tests is most helpful in establishing liver cell damage, since in the cases examined 67 variations in the results of the different liver function tests were encountered. The 147 cases with two or more pathologic liver function tests were divided into two groups:

(*a*) 81 cases belonging to the previously described group I (without thymol turbidity test).
(*b*) 66 cases belonging to group II in whom the thymol turbidity test was performed.

Six tests were necessary (cephalin-cholesterol flocculation, albumin/globulin ratio, cholesterol ester/cholesterol ratio, hippuric acid synthesis, plasma vitamin A, serum non-protein nitrogen) for the inclusion of all cases into Group I (figure 2). However, 72.8 per cent of the cases could have been accounted for by the albumin/globulin ratio and cephalin-cholesterol flocculation alone. The additional use of the cholesterol ester/cholesterol ratio increased the percentage of correct diagnosis. In only a few cases were additional tests needed.

In Group II also six tests were necessary to envelop all cases (cephalin-cholesterol flocculation, thymol turbidity, albumin/globulin ratio, urinary urobilinogen, cholesterol ester/cholesterol ratio and bromsulfalein retention). The majority (76.2 per cent) were correctly classified by the cephalin-cholesterol flocculation and thymol turbidity tests. The addition of the albumin/globulin ratio substantially increased the percentage of correct diagnosis (81.8 per cent) while additional tests were necessary in a few more cases.

2. Evaluation of diagnostic results.

Of the 151 cases comprising this group (L + B —) 148 remained in the medical jaundice group, while three proved to be surgical in nature representing patients with incomplete obstruction and associated liver damage in whom none of the signs of marked bile flow interference were positive on admission. Two factors were diagnostically helpful in directing these three cases from the medical to the surgical group:

(*a*) Fluctuating urinary urobilinogen levels as found by repeated qualitative or quantitative determinations of urinary urobilinogen in two cases. It is known that in calculous jaundice the urinary urobilinogen excretion may vary on consecutive days or longer periods from diminished to highly elevated levels.[28, 29] In one of these two cases a negative cephalin-cholesterol flocculation was an additional support.

(*b*) A mass in the gall-bladder region, suggesting a hydrops of the gall-bladder on the basis of cholelithiasis, directed the third case to the surgical group.

B. Cases with Marked Bile Flow Interference without Liver Cell Damage. Cases characterized by marked interference with bile flow and absence of significant liver cell damage belong primarily to the group of surgical jaundice.

1. Analysis of tests.

In 35 cases, one or none of the tests for liver function impairment and one or more of the tests for marked interference with bile flow were positive. In the majority of the cases only one of the latter tests and only rarely all four were positive. Marked bile flow interference was indicated in the majority of the cases by a markedly elevated alkaline phosphatase. The latter test together with the absence of urinary urobilinogen accounted for almost all cases in this group. Elevated total cholesterol levels added only a few remaining cases (figure 3). Demonstration of reduced fecal urobilinogen did

FIG. 3. Columns demonstrating the number of cases in whom marked interference with bile flow was correctly diagnosed by at least one positive test. They show the increase produced by taking into account additional tests.

not improve the grouping of these cases since fecal urobilinogen is usually reduced when urinary urobilinogen is absent. This statement can be generalized with the exception of the rare cases in which severe renal insufficiency due to chronic glomerulonephritis with deficient filtration may cause absence of urobilinogen from urine in the presence of urobilinogen in stool.[30, 31] In 24 of these 35 cases, one of the tests indicating liver cell damage was also positive. The test for liver cell damage most frequently positive was reversal of the albumin/globulin ratio (11 times).

2. Evaluation of diagnostic results.

Of the 35 cases, 32 proved to belong to the surgical and three to the medical group. One of two factors may divert such cases to the medical side.

(*a*) History of Treatment with Arsenicals as Part of an Antiluetic Therapy.

After such treatment jaundice may occur which is characterized by evidence of biliary obstruction but absence of detectable liver cell damage.[32] This represents a fairly acute condition in which both obstruction and normal liver cell function are seen at the onset of the disease. Of the three cases in our material, belonging to this category, one had a pathologic hippuric acid synthesis, another a positive thymol turbidity, while in the third case no indication for liver cell damage was found in any of the tests performed.

(*b*) Cholangiolitic Cirrhosis.

According to Watson and Hoffbauer,[33] after the defervescence of an acute hepatitis with typical liver cell damage, a protracted condition of normal liver cell function but marked interference with bile flow may occur which they designated as cholangiolitic cirrhosis. Such cases are recognized by a careful history and evaluation of clinical and biopsy findings. We had opportunities to study cases belonging to this category, but none were observed long enough to be used in the present analysis.

C. Cases Revealing Liver Cell Damage and Marked Interference with Bile Flow. In the material examined, there were 99 cases in whom at least two of the tests indicating liver cell damage and one of the tests indicating marked interference with bile flow were positive. Such cases, a priori, could be due either to a primary involvement of the liver or to an extrahepatic biliary obstruction associated with liver cell damage. In such instances, the results of the cephalin-cholesterol flocculation test served as the key criterion. This test has been described as permitting differentiation of surgical from medical jaundice in a relatively high percentage of cases since it is, as a rule, negative in the surgical group.[10, 19, 34, 35, 36, 37]

I. Group with Negative Cephalin-Cholesterol Flocculation Test

The negative cephalin-cholesterol flocculation test directed 38 cases of this group to the surgical side.

1. Analysis of tests.

In the majority of cases, only two of the tests indicating liver cell damage were positive (figure 4). The tests most commonly giving pathologic results were the albumin/globulin ratio, thymol turbidity and the cholesterol ester/cholesterol ratio. In most of the cases, two or three of the tests indicating marked bile flow interference were positive. In almost all of them, the serum alkaline phosphatase was markedly elevated, while urinary urobilinogen was absent in about two-thirds of the cases.

2. Evaluation of diagnostic results.

The presence of liver cell damage in these cases which presented both marked bile flow interference and negative cephalin-cholesterol flocculation will first suggest a biliary hepatitis, i.e., liver cell damage produced by protracted biliary obstruction.[38, 39] The development of biliary hepatitis depends upon the degree and the duration of the obstruction and is, there-

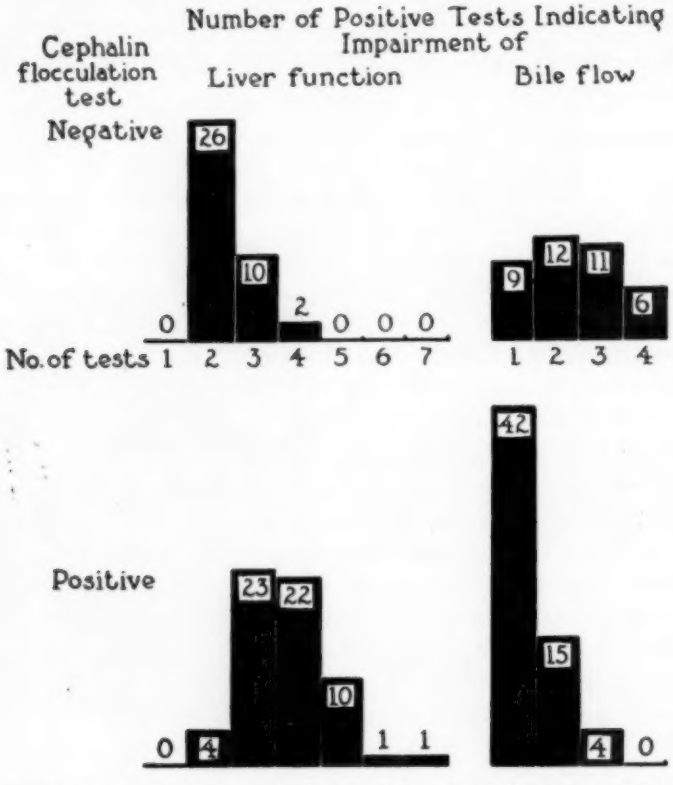

FIG. 4. Number of patients (indicated by black column) with evidence of liver cell damage and marked interference with bile flow, revealing pathologic results in a given number of liver function tests. The cases are separated according to the results of the cephalin-cholesterol flocculation test.

fore, more commonly seen in complete obstruction due to tumors than in incomplete obstruction due to stones. This is also borne out by the incidence in this series since 19 of the 33 cases remaining on the surgical side were due to malignant obstruction. Common exceptions to the rule that a negative cephalin-cholesterol flocculation is indicative of surgical jaundice are about 30 per cent of the cases of toxic hepatitis.[38] If in the latter, the laboratory tests indicative of marked interference with the bile flow are positive, these cases are presumptively directed into the surgical group. However, evidence of a toxic etiologic factor should direct them to the

medical side. In problematic cases, the histologic picture as seen in biopsy specimens may help in the differential diagnosis between toxic hepatitis and extrahepatic obstructive jaundice. In our material five such cases were met. Their histories revealed either exposure to arsenicals or sulfonamides, acute alcoholism, or preceding pneumonia. In all these cases, two of the tests for liver cell damage and one or two of the tests for marked bile flow interference were positive. In two of them, the non-protein nitrogen was elevated, as often seen in patients with toxic hepatitis.[40]

II. Group with Positive Cephalin-Cholesterol Flocculation Tests

Positive cephalin-cholesterol flocculation diverted 61 cases to the medical side since a priori such cases should be considered as primary hepatitis with marked interference with bile flow.

1. Analysis of tests.

In the majority of these cases (figure 4) three or four tests indicative of liver cell damage gave pathologic results and in contrast to the previous group often five or more were positive. In addition to the cephalin-cholesterol flocculation, the albumin/globulin ratio, thymol turbidity and cholesterol ester/cholesterol ratio were most often positive. In contrast to the group with negative cephalin-cholesterol flocculation, marked bile flow interference was here primarily indicated by absence of urinary urobilinogen (46 out of 61), whereas the total serum cholesterol and serum alkaline phosphatase were less often markedly elevated.

2. Evaluation of diagnostic results.

Positive results of tests indicative of marked interference with the bile flow (in the presence of liver cell damage) should first suggest intrahepatic biliary obstruction as may occur in any type of acute (infectious or toxic) hepatitis or of cirrhosis. This phenomenon, at least in certain stages of hepatitis, is relatively frequent.[33, 41, 42, 43] However, there are certain exceptions to this assumption:

(*a*) Purulent Hepatitis.

In cases of extrahepatic mechanical biliary obstruction, either an ascending or more commonly a hemolymphatic infection of the portal triads may lead to what has been called purulent hepatitis associated with liver cell damage.[38, 44] This condition is not dependent upon duration or degree of the obstruction but rather upon the presence of a complicating infection. It is therefore more often a complication of benign rather than of malignant obstruction, found especially in cholelithiasis and cholecystitis. In such instances, the cephalin-cholesterol flocculation is or may become positive in a case of surgical jaundice. Obviously, such conditions will at first fall into the group of medical jaundice. They can be diverted to the surgical

side, where they belong, by the clinical evidence of a bacterial infection, i.e., fever, chills and leukocytosis, and by the typical histologic picture of the liver biopsy specimen. In our material nine cases were thus brought to the surgical side, despite liver function tests similar to those of the medical cases. One of those nine cases, despite the characteristic findings of a septicemia, did not belong in the surgical group: it represented one of the rare instances of a protracted cholangiolitis without obstruction but with transition into cirrhosis. The results of the liver biopsy as well as the fact that almost all tests indicating liver cell damage were positive brought this case back to the medical side.

(*b*) Biologically false positive tests.

There are rare instances of biliary hepatitis without complicating infection which have a positive cephalin-cholesterol flocculation test and which could possibly be considered as false positive. In two cases in our series such possibilities arose. They or similar ones might be correctly diagnosed by the palpatory findings in the abdomen (mass), signs of metastases, history of repeated attacks, roentgen-ray findings, etc.

Evaluation of Tests Indicative of Liver Cell Damage

The follow-up of a large number of jaundiced patients with established diagnosis permits an evaluation of the liver function tests. It has been postulated above that in general at least two of the tests indicating liver cell damage should be positive for such damage to be entertained. This was done because practically every one of the function tests used may occasionally yield biologically false results; usually without available explanation. In four of the examined jaundice cases, however, liver cell damage had to be conceded because of clinical findings although only one of the tests for liver cell damage was positive.

The question now arises which of the tests should be selected from experience gained in practical use. Some information concerning this question was provided by the results of function tests in the above discussed smaller group of cases with liver cell damage but without marked bile flow interference. Now, all cases showing positive results in at least two tests indicating liver cell damage will be considered. These 246 cases were also divided into the two groups mentioned: Group I in which the thymol turbidity test was not performed and Group II in which this test was performed. In 135 cases of Group II (table 3) a combination of the thymol turbidity test with either the cephalin-cholesterol flocculation or the albumin/globulin ratio permitted recognition of liver cell damage in two-thirds of the cases. A combination of the cephalin-cholesterol flocculation plus the albumin/globulin ratio permitted this in a slightly smaller number. In the above percentages, results of other tests are not considered. If two positive results in all three above-mentioned tests were accepted, 83 per cent of the cases

TABLE III

Percentage of Cases with Liver Cell Damage Correctly Grouped on Basis of at Least Two Positive Tests for Liver Cell Damage, and the Increase in This Percentage Due to Inclusion of Additional Tests

With Thymol Turbidity Test	Cases Examined Per Cent	Without Thymol Turbidity Test	Per Cent
Cephalin-cholesterol flocculation plus albumin/globulin ratio	61.7		
Thymol turbidity test plus albumin/globulin ratio	66.0		
Cephalin-cholesterol flocculation plus thymol turbidity test	66.7	Cephalin-cholesterol flocculation plus albumin/globulin ratio	69.4
Cephalin-cholesterol flocculation plus thymol turbidity test plus albumin/globulin ratio*	83.6	Cephalin-cholesterol flocculation plus albumin/globulin ratio plus cholesterol ester/cholesterol ratio	84.7
The above tests plus cholesterol ester/cholesterol ratio	93.3	The above tests plus oral hippuric acid	92.8
The above tests plus urinary urobilinogen	98.5	The above tests plus non-protein nitrogen	97.3
The above tests plus bromsulfalein	99.2	The above tests plus vitamin A	98.2
The above tests plus oral hippuric acid	100.0	The above tests plus bromsulfalein	99.1
		The above tests plus urinary urobilinogen	100.0

* For instance pathologic results in cephalin-cholesterol flocculation and in albumin/globulin ratio but normal in thymol turbidity, or as another example all 3 being positive.

were correctly classified. The addition of the cholesterol ester/cholesterol ratio, i.e., at least two positive results in four tests, raised the percentage further to a significant degree. The additional consideration of the results of urinary urobilinogen determination, bromsulfalein retention or hippuric acid synthesis added only a few more cases. On this basis, it appears that, in the vast majority of the cases, liver cell damage can be diagnosed with four tests: cephalin-cholesterol flocculation, thymol turbidity, albumin/globulin ratio and cholesterol ester/cholesterol ratio. However, for correct evaluation of all of the cases in our material three more tests were necessary.

The great significance of the thymol turbidity test is indicated by comparing the above group with 111 cases of Group I which were observed before the thymol turbidity test was available. In the latter cases, the majority were "diagnosed" by the cephalin-cholesterol flocculation, the albumin/globulin ratio, the cholesterol ester/cholesterol ratio and hippuric acid synthesis whereas five additional tests were required to diagnose the remaining four cases. In our material, therefore, the thymol turbidity test reduced the number of other more complicated tests required to group the cases correctly. Additional flocculation tests may possibly further reduce the necessity for the more complicated tests and thus simplify the differential diagnosis of jaundice.

In no case were all tests indicative of liver cell damage positive (figure 5). In most instances, two to four tests were positive, whereas a higher number was rarely encountered even in severe cases.

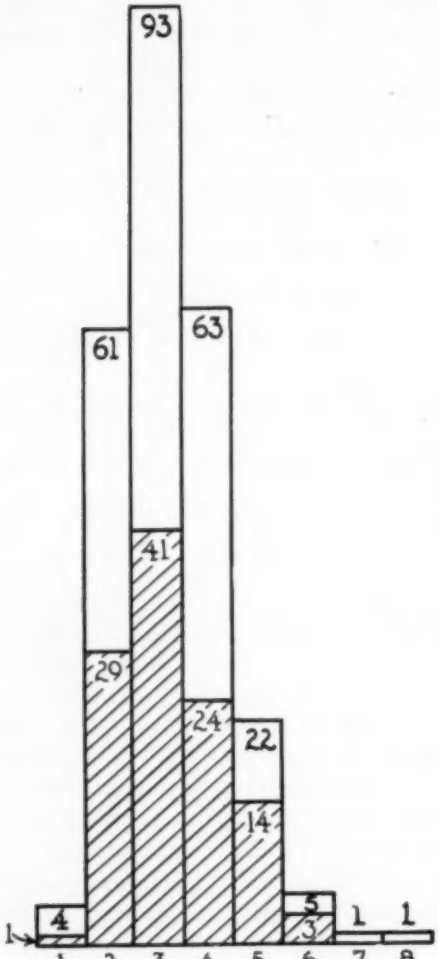

FIG. 5. Columns indicating the number of cases in whom a given number of tests indicative of liver cell damage were positive. The cross hatched part of the columns represents patients in whom no thymol turbidity tests were performed.

EVALUATION OF TESTS FOR MARKED BILE FLOW INTERFERENCE

One test denoting marked bile flow interference was considered sufficient to indicate that phenomenon. On this basis, the latter was diagnosed in 134 cases. In one-third of them absence of urinary urobilinogen was the only positive test; in combination with other tests, this absence was demonstrable in two-thirds of the cases (table 4). Marked elevation of the serum alkaline phosphatase alone was found in a relatively small percentage. If one positive test in the determination of either urinary urobilinogen or of serum alkaline

TABLE IV

Percentage of Cases with Marked Interference with Bile Flow Correctly Grouped on Basis of Single or Groups of Tests Denoting Marked Bile Flow Interference

Absence of urinary urobilinogen alone	29.8%
Serum alkaline phosphatase elevation alone	16.4%
Total serum cholesterol elevation alone	5.3%
All cases showing absence of urinary urobilinogen	67.1%
All cases showing absence of urinary urobilinogen and/or elevation or alkaline phosphatase	94.7%
All cases showing absence of urinary urobilinogen or elevated alkaline phosphatase or elevated cholesterol or combination of them	100.0%

phosphatase or of both was used as criterion, almost all cases of this group were accounted for. Only a few more were included because of a markedly elevated total cholesterol. In only 17 per cent of the cases were all three tests positive. The determination of the fecal urobilinogen added little in this type of analysis.

COMMENT

This study attempts first to analyze the thought processes used in the differential diagnosis of jaundice based primarily upon laboratory determinations, and secondly, to evaluate the liver function tests from the practical point of view by deliberately giving less emphasis to their physiologic meaning. The teaching of clinical diagnosis might be considered as the presentation of analytic thought processes which lead over various "crossings" to the correct diagnosis. In this study, an attempt was made to illustrate graphically such analytic thought processes in a case of jaundice (figure 1). The main "crossings" were provided by (1) liver cell damage, (2) marked interference with bile flow and (3) results of the cephalin cholesterol flocculation reaction in the cases in which the two former were positive. Further "crossings" were based on a history of exposure to hepatoxic substances especially the arsenicals—pointing to a toxic hepatitis. Similarly, septic manifestations served to separate the purulent hepatitis with positive cephalin-cholesterol flocculation from primary hepatitis with marked interference with bile flow. The presence of an abdominal mass, or a history typical of biliary colics helped in the recognition of the cases in which the cephalin-cholesterol flocculation reaction might be considered as biologically false positive. In some instances, the result of the liver biopsy may be the only criterion directing the case into the right group.

As mentioned previously, we did not initially diagnose all cases correctly. Some were put in this schematic arrangement by hindsight rather than foresight. Obviously, even in following the described lines, one may not always reach the correct diagnosis at first.

In evaluating liver function tests, one should be aware of the fact that almost every one of them may occasionally yield a pathologic result if done on a large series of so-called normal controls. Such pathologic results have to be considered biologically false positive since no other evidence for liver function impairment exists, either on the basis of clinical or other laboratory

examination. There is probably a biologic reason for the positive results in such instances, but it is apparently not related to the liver. This reason may be obvious in instances of pathologic albumin/globulin ratio or non-protein nitrogen levels, but is usually obscure in the case of cephalin-cholesterol flocculation or thymol turbidity. The term biologically false positive is used in analogy with the sero-diagnosis of syphilis where it applies to positive reactions in the absence of syphilis. According to the presented concept, the cephalin-cholesterol flocculation reaction is negative in obstructive jaundice with and without biliary hepatitis, except in the purulent form. It is positive in most types of primary hepatitis and cirrhosis. To allow for biologically false positive results, consideration of an abdominal mass, or typical history had to be introduced. Moreover, the possibility of biologically false positive tests was the reason for insisting on two positive tests as indicative of liver cell damage. It should be stressed that not too often were more than three tests for liver cell damage positive, even in quite severe cases of hepatitis. Similarly only in relatively few instances were all tests indicating marked bile flow interference positive.

The number of positive tests in a patient without consideration for their individual physiologic basis is apparently of some significance. The higher the number of positive tests the more marked is the liver cell damage. As long as the physiologic basis for many of the tests remains obscure, such an assumption may be helpful. Thus, for instance, in the group in which both liver cell function and bile flow were impaired, the sub-group with positive cephalin-cholesterol flocculation, which as a whole presents primarily medical jaundice, had a much higher number of positive tests than the sub-group with negative flocculation in which biliary hepatitis is prominent. In the latter group more of the tests indicating marked bile flow interference were positive, whereas in the former group, only urinary urobilinogen was absent in most instances. Since this absence is only temporary, serial observations of urobilinogen excretion would eliminate many cases from this group and line them up with uncomplicated cases of medical jaundice which showed only liver cell damage on admission.

There may also be biologically false positive results in the tests indicating marked bile flow interference. Obviously, the total cholesterol may be elevated due to reasons not connected with the jaundice and the serum alkaline phosphatase may be markedly increased, e.g., due to bone lesions. However, these factors are readily recognized by clinical observation. In the presence of jaundice, therefore, one positive test for marked bile flow interference is sufficient, provided other disturbing factors are taken into account.

In reviewing the entire material, one is struck by the frequent concurrence of both liver cell damage and marked bile flow interference (34.7 per cent of the cases). This indicates that the usually held premise from which this study also started, namely, that medical jaundice has only liver cell damage, and surgical jaundice as a rule only marked bile flow interference

is incorrect in a significant number of cases. Of the medical cases, 26.3 per cent were complicated by marked interference with the bile flow, something of the nature of what has been previously called intrahepatic biliary obstruction. In the majority of cases with surgical jaundice (60 per cent) liver cell damage was found. The latter was due in 47.5 per cent to biliary hepatitis (secondary liver cell damage due to prolonged obstruction) and in 12.5 per cent to purulent hepatitis caused by bacterial infection of the portal triads. Nevertheless, the above-mentioned premise proved to be a good starting point for a diagnostic analysis.

On the basis of the material presented here, the performance of the following liver function tests can be recommended for the differential diagnosis between medical and surgical jaundice: cephalin-cholesterol flocculation, thymol turbidity, albumin/globulin ratio, cholesterol ester/cholesterol ratio, urinary urobilinogen and serum alkaline phosphatase. To group all cases, it may be advantageous to add the bromsulfalein retention and the hippuric acid synthesis.

Obviously, more laboratory determinations than these considered in this study are in clinical use, e.g., urinary and serum bilirubin, galactose tolerance test, total serum protein (especially for control of therapy), urinary amino acid excretion, prothrombin time and sedimentation rate. They give important information and may determine the diagnosis in some patients. Most of them were determined in our cases, but were omitted from the discussion for the sake of simplicity. It should also be stressed that only the initial determination was taken into account and that, for instance, the follow-up of the serum bilirubin concentration was not taken into consideration. Similarly, the degree of alteration from the normal was not considered. Thus the thymol turbidity, although positive in a significant number of cases of surgical jaundice, seldom rises above 10 units in the latter condition, in contrast to medical jaundice.

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Summary

It is attempted to present a schematic plan of the thought processes applied in the differential diagnosis between medical and surgical jaundice. It uses primarily laboratory findings but takes into account, to some extent, clinical history and/or physical findings. It is based primarily upon the recognition of liver cell damage and marked interference with the bile flow. The cases revealing both are further subdivided by the results of the cephalin-cholesterol flocculation test.

The analysis of these thought processes provides an opportunity for evaluating the efficiency of the liver function tests for practical purposes without emphasis upon their physiological basis. It appears that at least two positive tests are necessary to establish liver cell damage, but only one to recognize marked bile flow interference. Only rarely are all tests indicating either of the two phenomena positive and the number of positive tests appears to parallel the severity of the pathologic process.

The overwhelming majority of cases will be guided into the right direc-

tion if cephalin-cholesterol flocculation, thymol turbidity, albumin/globulin ratio, total serum cholesterol, and cholesterol esters, serum alkaline phosphatase and urinary urobilinogen are determined. The addition of the hippuric acid synthesis and bromsulfalein retention tests permitted, in the final evaluation, correct grouping of all cases in this series.

The addition of the thymol turbidity test has markedly decreased the need for the more complicated liver function tests in the differential diagnosis of jaundice. It may, therefore, be expected that additional flocculation or precipitation tests may further simplify the laboratory diagnosis of jaundice.

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LOEFFLER'S SYNDROME AND PULMONARY INFILTRATIONS ACCOMPANIED BY PERIPHERAL EOSINOPHILIA *

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IN the past several years reports have appeared in the American literature on patients with pulmonary infiltration accompanied by blood eosinophilia. In 1932 Loeffler [1] first described a syndrome characterized by these two signs. By 1940, 105 [2] cases had been reported in the literature, 51 of these by Loeffler.[3] Most of the cases since then have come from the central European area. In 1945, Miller [4] reported one case and could find but four similar cases reported [2, 5, 6, 7] in this country. More and more attention has been given recently to pulmonary infiltrations with blood eosinophilia, climaxed by an editorial in the Journal of the American Medical Association.[8] However, there has been a general tendency to associate any case having pulmonary infiltrations and blood eosinophilia with the syndrome described by Loeffler.

Loeffler's original description is worthy of note. The principal finding is a pathological shadow in the roentgenogram of the chest. This is variable and may be bilateral or unilateral, large or small, simple or multiple, homogeneous or spotty. It may appear at any site and have any extent. The most important feature is its fleeting character. It decreases in size and intensity in from three to eight days. Other similar shadows may appear in different regions of the lungs in rapid succession.

The eosinophilia varies widely from very slightly above normal to 60 per cent in some cases. The degree of eosinophilia and extent of the pulmonary changes show no parallelism. The height of the eosinophilia tends to occur after the maximal pulmonary infiltrations. Over 25 per cent of Loeffler's cases were discovered on routine roentgenographic examination. As a rule the patients have few and minor symptoms, and only slight elevation of temperature. Over 60 per cent of the patients were entirely afebrile in Loeffler's series. Cough is relatively frequent and can be severe. Sputum is usually absent or slight with mucoid, frothy consistency. A small pleural effusion or friction rub has at times given evidence of occasional pleural involvement, which would explain the occurrence of chest pain. Abnormal physical signs over the lung fields are few and in general consists of occasional moist râles. Some seasonal incidence is noted in that most of the cases were found in July and August. The course is always benign. The patients usually do not suffer more than slight disturbances of their general condition.

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An adequate explanation of the etiology and pathological picture is lacking. Loeffler believed that the eosinophilia could not be considered either as an expression of an anaphylactic process or the result of parasitic infection. He likewise discarded the assumptions of some authors that the lung changes were due to emboli, localized bronchial asthma, or atelectasis. He said that at times the infiltrations are differentiated only with difficulty from early tuberculous infiltration or from genuine pneumonia, and he emphasized that repeated roentgenograms were necessary to make a diagnosis. In none of his cases was tuberculosis demonstrated, although one of his cases developed tuberculosis one year later. In 35 per cent of his cases the tuberculin test was negative. He emphasized five characteristics of the syndrome: (1) infiltrations shown by roentgenogram, (2) fleeting and changing character, (3) eosinophilia, (4) mild degree of illness, (5) short duration.

We have observed three cases recently with pulmonary infiltrations and blood eosinophilia. All of them showed interesting clinical findings.

Case Reports

Case 1. E. B., a 19 year old white student nurse, was first admitted to the Rhode Island Hospital April 4, 1944 with the chief complaint of malaise and headache of eight hours' duration. There was no history of any chest pain, sore throat or cough. Past history was entirely negative.

Family history revealed that her brother and sister had had symptoms of hay fever during the months of August and September for the past three years.

Review of systems was non-contributory.

Physical Examination. Blood pressure was 110 mm. Hg systolic and 80 mm. diastolic, temperature 100.2° F., pulse 128, respirations 28. The patient was a well-developed and well-nourished white female in no apparent distress, holding an icebag to her head. The pharynx was slightly injected. There were a few posterior cervical glands palpable. The lungs were clear to auscultation and percussion. The heart was not enlarged and showed a regular mild tachycardia. Her skin was warm and moist, and a diagnosis of mild influenza was made.

Laboratory Data (day of admission). Urine: Specific gravity 1.018, contained no red blood cells, a few white blood cells, no casts, albumin and sugar negative. Blood: White blood cells 27,000 (87 per cent neutrophiles, 4 per cent lymphocytes, 8 per cent monocytes, 1 per cent eosinophiles), 4,610,000 red blood cells, blood urea nitrogen 16 mg. per cent.

Hospital Course. The patient experienced a bad initial night and developed a dry, hacking cough. Her temperature rose to 102° F. Examination of the lungs revealed medium crepitant râles in the left upper posterior chest. Later on the same day, the patient appeared moderately ill, and became dyspneic. Examination of the chest at this time revealed crepitant râles which were heard over both anterior chests, more pronounced in the upper right. The white blood count had risen to 31,950. A roentgenogram of the chest (figure 1) revealed extensive density throughout both lungs, most marked at the bases, and consistent with a diffuse pneumonitis. There was no fluid present in the pleural cavities. The diaphragm and heart shadow appeared normal. A blood culture and sputum examination were obtained and the patient was started on sodium sulfadiazine five grams by mouth. This instituted vomiting, the sulfadiazine was discontinued, and sulfamerazine was given, one gram every four hours.

On the third hospital day the patient was somewhat irrational. Her temperature rose to 103° F., pulse 140, and respirations 40. During the afternoon she suddenly had a severe attack of dry, hacking cough, cyanosis and dyspnea. She was put immediately into a Burgess oxygen tent with some relief. Nose and throat cultures revealed no pathogenic organisms. Her white count, at this time, was 30,250, with 88 per cent neutrophiles. The sputum was negative for pneumococcal typings.

On the fourth hospital day sputum examination remained negative. Sulfamerazine blood level was 12.93 mg. per cent. A repeat roentgenogram of the chest showed

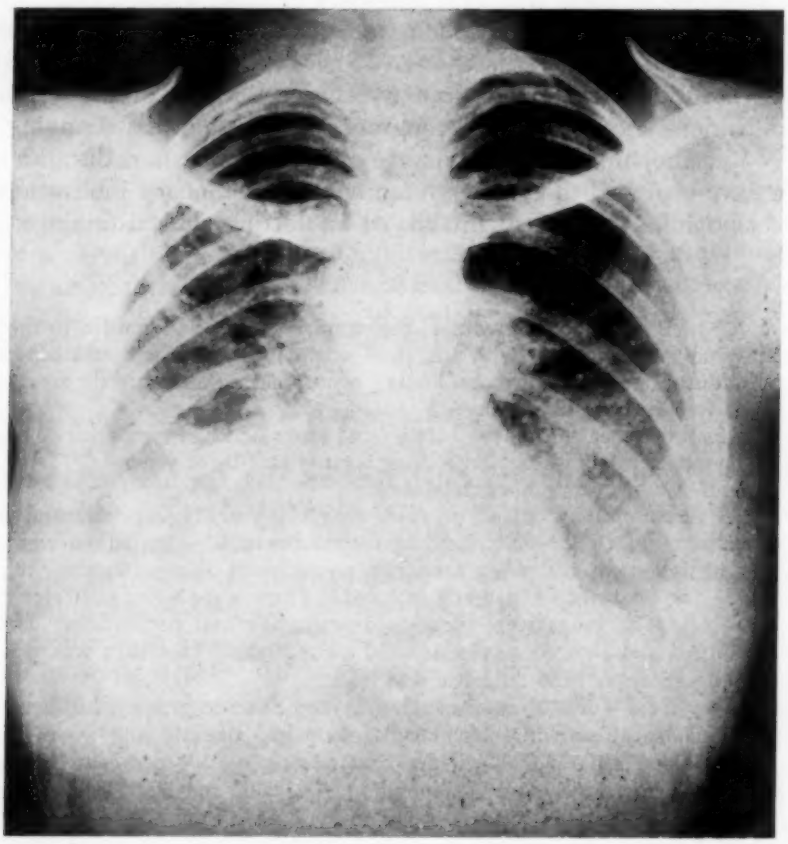

FIG. 1. Roentgenogram of chest in Case 1. It showed extensive density throughout both lungs most marked at the bases.

findings much the same as in the previous one, with a diagnosis of an acute bronchopneumonia. The patient continued to have a dry, hacking cough and became more dyspneic. During that night she suddenly became very cyanotic, apneic and appeared lifeless. Artificial respiration was immediately started and continued for a length of time necessary to prepare 20 c.c. of a solution containing 7.5 grains of aminophylline. This was given intravenously, and after about 15 c.c. had been injected, the patient suddenly started to breathe spontaneously. Oxygen under positive pressure and a helium-oxygen mixture were tried but the patient did not tolerate either. She was kept in an oxygen tent. Examination of the chest continued to reveal fine râles which shifted.

On the sixth hospital day she began to raise a little mucoid sputum, sometimes blood-tinged. This showed no pathogenic organism on culture or smear. A portable roentgenogram of the chest (figure 2) showed accentuation of the lung markings and diffuse mottled density throughout both lungs with marked increase in the process compared with that of the previous films. The white cell count was 22,250, with 88 per cent neutrophiles, 7 per cent lymphocytes, 2 per cent monocytes, and 3 per cent eosinophiles. On the seventh hospital day it increased to 31,800, with 89 per cent

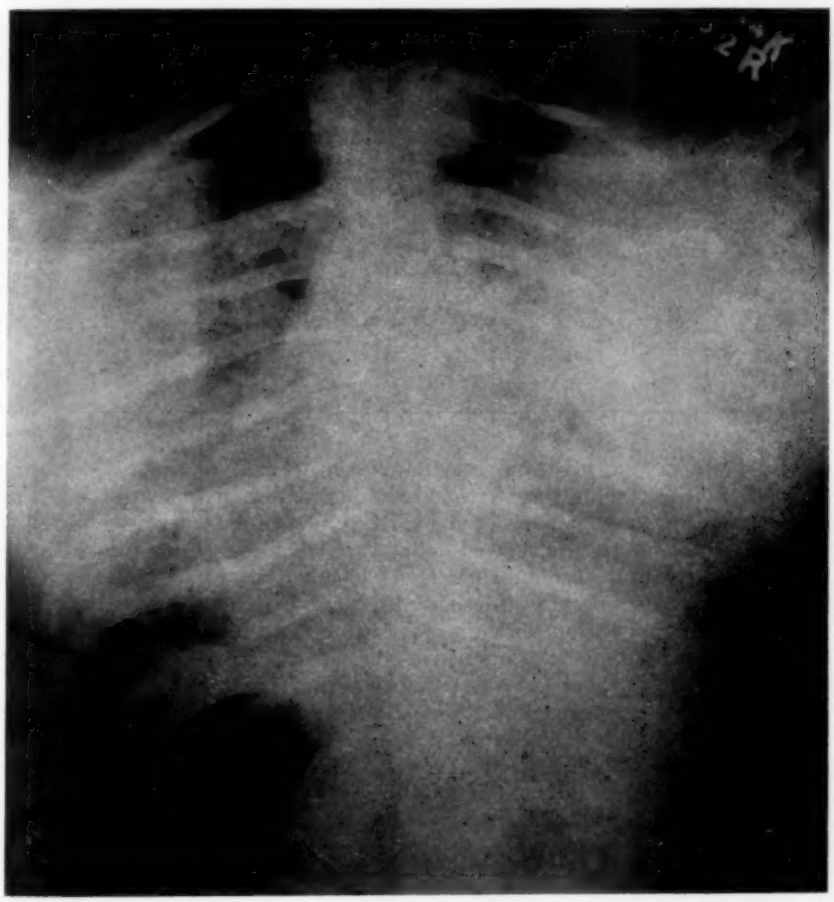

FIG. 2. Roentgenogram of chest in Case 1 on the sixth hospital day. It showed accentuation of the lung markings and a diffuse, mottled density throughout both lungs with a marked increase in the process compared to previous films.

neutrophiles (table 1). Her temperature had remained elevated throughout her course in spite of sulfonamide therapy. Repeated blood cultures remained sterile. Examination of the lungs showed high pitched breath sounds and coarse râles at the right base especially in the axilla, with diminished breath sounds over the left lower posterior chest. On the eighth hospital day the white count remained elevated but with an increase of eosinophiles to 10 per cent. Agglutination tests were negative for typhoid O and H, paratyphoid A and B, undulant fever, and proteus OX19.

TABLE 1

Summary of Data

Date	Temperature F.	White Cell Count	Neutrophiles %	Differential Count		Eosinophiles %	Sedimentation Rate mm. per hour
				Lymphocytes %	Monocytes %		
4/ 5/44	102.0°	27,700	87	4	8	1	
4/ 7/44	103.0°	30,250	88	10	2	0	
4/11/44	101.0°	31,800	89	10	1	3	
4/12/44	102.4°	25,800	80	10	0	10	48
4/15/44	98.6°	23,300	43	12	2	41	
4/17/44	98.8°	14,950	68	12	2	18	
4/21/44	98.8°	7,950	60	28	5	7	48
5/ 2/44	98.8°	9,900	57	31	7	5	34
2nd Admission							
5/17/44	102.0°	18,600	84	12	4	0	10
		10,150				0	
3rd Admission							
10/30/45	99.0°	16,900	70	24	5	1	
11/ 2/45	100.6°	14,250	70	16	13	1	40
11/ 3/45	102.6°	17,250	71	16	9	4	
11/ 8/45	103.0°	23,150	81	19	0	0	
11/16/45	98.6°	9,600	65	28	6	1	11

On the ninth hospital day the patient was somewhat disoriented. Her temperature was 102.4° F. During the afternoon she had a second sudden attack of apnea and cyanosis which was again relieved by 7.5 grains of intravenous aminophylline. Examination of the lung fields showed dullness, harsh breath sounds, and diminished vocal and tactile fremitus over the right lower lobe, posteriorly. Repeat examination of the chest by roentgenogram still showed extensive increased density throughout both lungs and in comparison with the previous films showed some clearing of the process. There was no evidence of fluid in the pleural cavities.

On the eleventh hospital day the patient's white count was 23,300, with 43 per cent neutrophiles, 12 per cent lymphocytes, 2 per cent monocytes, 41 per cent eosinophiles. A nasal smear revealed 10 to 12 eosinophiles per high dry field.

On the fifteenth day a repeat examination of the chest by roentgenogram showed a diffuse cloudy opacity and mottled infiltration throughout both lungs, but there was a continued clearing and improvement of the process in comparison with the previous films.

On the seventeenth hospital day the white count was 7950, with 7 per cent eosinophiles. She was taken out of oxygen and continued to improve and feel much better. On the twentieth hospital day her temperature returned to normal. Sulfamerazine was discontinued on the twenty-second hospital day. Patient continued to improve and examination of the lung fields at this time showed no abnormalities. However, repeat roentgenographic examination showed accentuation of the hilar shadows and cloudy opacity in the lower halves of both lung fields. Comparison with the previous films showed considerable clearing of the process.

Sedimentation rate at this time was 34 mm. in one hour, and her white count had dropped to 9900, with 5 per cent eosinophiles. The patient improved and was discharged on the forty-first hospital day. Examination of the chest by roentgenogram (figure 3) at this time showed slight accentuation of the hilar shadows and markings, but the lung fields were clear and showed no residual density or other pathologic

process. Repeated sputum examinations were negative for acid fast bacillus; skin tests for tuberculosis and brucellosis were negative, as were stools for ova and parasites.

Second Hospital Admission: The patient was readmitted May 16, 1944. One day previous she had weakness and went to bed. Her temperature was 100.8° F.

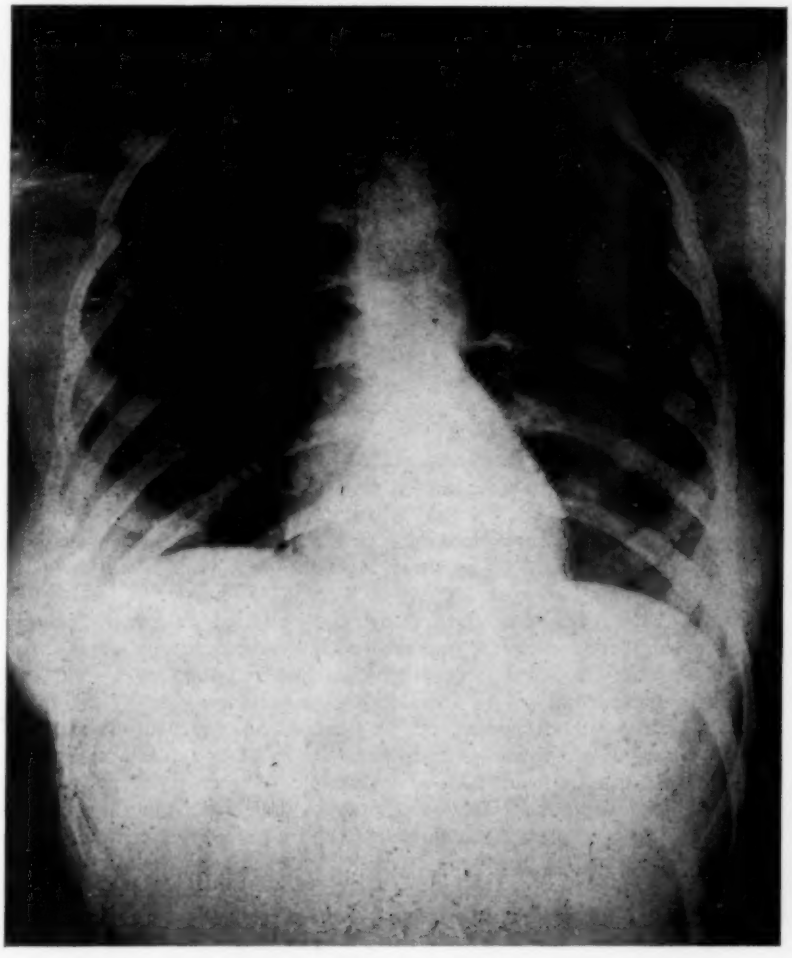

FIG. 3. X-ray of chest of Case 1 on fortieth hospital day. It showed slight accentuation of the hilar shadows and markings but the lung fields were clear.

She felt similar to her previous admission, with malaise, headache, and generalized aching.

Physical examination at this time was essentially negative.

Laboratory Data. Her white blood count at this time was 18,900, with 84 per cent neutrophiles, 12 per cent lymphocytes, and 4 per cent monocytes. Temperature on admission was 102° F. Roentgenogram of the chest showed clear lung fields with no evidence of recurrence or residual density in the lungs. Blood culture was sterile and a repeat white blood count was 10,150 with no eosinophiles. Electro-

cardiogram showed a slight sinus arrhythmia. Rate was 112. Conduction time was within normal limits. The T-waves were all upright except T_3 which was diphasic. Chest fluoroscopy at this time showed the lung fields to be clear and diaphragmatic excursions and cardiac silhouette within normal limits. Skin tests with 24 common allergens at this time were negative. The patient improved and was discharged.

Third Hospital Admission: October 30, 1945.

Interval Note. The patient had been in good health since her last hospitalization until 48 hours before present admission. At that time she began to feel tired and had a mild sore throat which gradually became worse. She developed a cough productive of small amounts of greenish and brownish sputum. She had no chills or noticeable fever, and no pain in her chest. The patient developed a headache on the day of admission. She noticed some pain on swallowing.

Physical examination showed a well-developed, well-nourished woman in no acute distress. She was coughing occasionally. Temperature 99.6° F., pulse 90, respirations 24. Except for moderate injection of the posterior pharynx, the physical examination was essentially negative. The lungs were normal to examination, and no râles were heard.

Laboratory Data (on admission). Urine was normal. Blood: White blood count 16,900, with 70 per cent neutrophiles, 24 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophiles. Hemoglobin 15 grams, glucose 74 mg. per cent.

A chest roentgenogram showed in the left upper lung field a small patch of faint haziness at the level of the third rib anteriorly, and localized somewhat laterally. The remainder of both lung fields was clear.

On the second hospital day her temperature rose to 100.6° F. She was coughing rather severely and still complained of pain on swallowing. The pharynx was moderately injected. She was started on 20,000 units of penicillin every two hours intramuscularly. Her temperature remained elevated, and the patient had difficulty in swallowing because of pain. The chest revealed no abnormalities by percussion and auscultation. The white count was 14,250, with 70 per cent neutrophiles. A throat culture was negative for hemolytic streptococcus. Penicillin was discontinued at this time. A repeat chest roentgenogram showed the right lung field clear throughout. On the left side there was some faint patchy haziness in the upper lung extending from the level of the second rib to the third interspace anteriorly. The remainder of the fields was clear. The appearances in the left side were interpreted as being consistent with an atypical bronchopneumonia. Sheep cell agglutinations were negative. At this time the patient did not seem very ill. Numerous crepitant râles were heard over both lower lung fields on the ninth hospital day. On the tenth day her white count was 23,150, with an increase in neutrophiles to 81 per cent. A roentgenogram in comparison with the previous one taken November 2, 1945, showed some mottling throughout the lower half of the right lung field. Similar fine mottling was seen throughout the left lung lobe in addition to practically the same irregular patches of peripheral haziness previously noted in the upper left field.

During the next five days her temperature remained normal. Examination of the chest revealed much clearing, although scattered râles over both bases were still present. She continued to improve and was discharged. The chest roentgenogram two months later showed no residual pathological signs. During the next year she remained free of all symptoms and her chest roentgenogram remained negative.

Case 2. H. N., a 49 year old white cook, was admitted to the Rhode Island Hospital June 9, 1945. The patient's present illness dated back about two months when she noticed a pain in her upper chest on such exertion as going upstairs and going about her duties as cook. She had also noted marked shortness of breath on exertion. Her appetite had been poor and she had a mild non-productive cough. These symptoms had become progressively worse and the location of the pain had become centered in the precordial area with radiation into the neck.

Past history was essentially negative. She had always been an active and apparently healthy individual.

Family history was essentially negative.

Review of systems was essentially normal except for present illness.

Physical examination revealed a well-developed, well-nourished woman not appearing ill. Her color was good and respirations were quiet. Blood pressure was 120 mm. Hg systolic and 70 mm. diastolic, temperature 101.6° F., pulse 100, respirations 24. Her pupils were round and regular and reacted to light. The throat was not injected. Her tongue was slightly coated. The heart was slightly enlarged to percussion. The first sound at the apex was somewhat accentuated and snapping and there was a soft systolic murmur at the apex. No diastolic murmurs could be heard. The abdomen was lax, with no masses, spasm, or tenderness. Her lungs were clear and resonant throughout.

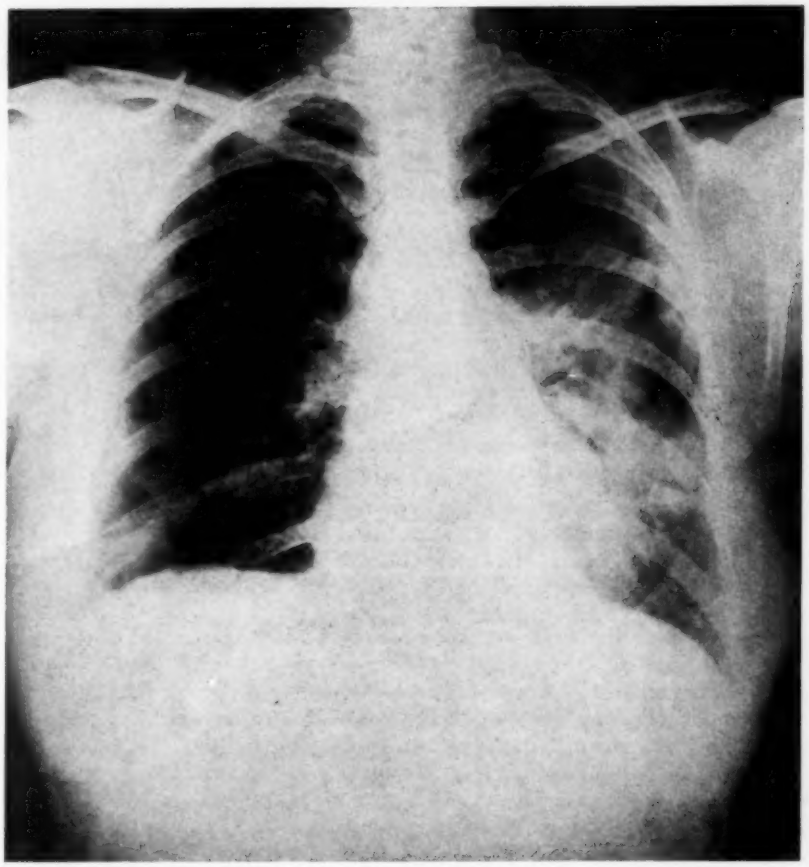

FIG. 4. Initial roentgenogram of chest in Case 2. It showed thickened markings at the base of the right lung with dense streaks projecting laterally over the axillary portion of the ninth rib. On the left side there was a patchy, irregular density through the middle two-thirds of the lung from the fifth interspace to the ninth rib posteriorly.

Laboratory Data (on admission). Red blood count 4,080,000, hemoglobin 12.9 gm., white blood count 14,900, with 32 per cent neutrophiles, 23 per cent lymphocytes,

42 per cent eosinophiles. Blood urea nitrogen 8 mg. per cent. Agglutination tests were negative for typhoid H and O; paratyphoid A and B; undulant fever and proteus OX19. The sputum showed no acid fast organisms. A roentgenogram of the chest (figure 4) showed mild enlargement of the left ventricle of the heart. The aortic arch was negative. At the base of the right lung there were thickened markings with some dense streaks projecting laterally over the axillary portion of the ninth rib. On the left side there was a patchy, irregular density through the middle two-thirds of the lung from the fifth interspace to the ninth rib posteriorly. The markings in this neighborhood were irregularly thickened. The basal portion of the lung was negative. The interpretation was that this was consistent with a recent pneumonic process. The possibility of neoplasm could not be excluded. The shadow in the right base was suggestive of a healing infarct.

Course in Hospital. She was essentially asymptomatic in bed. She gave no history of any allergic mainfestations or of any worm infection. Repeated sputum examinations were negative for acid fast organisms. The urine remained negative. Her stools were negative for ova and parasites. Her blood picture is revealed in table 2.

TABLE II

Summary of Data

Date	Temperature F.	White Cell Count	Neutrophiles %	Differential Count		Eosinophiles %	Sedimentation Rate mm. per hour
				Lymphocytes %	Monocytes %		
6/11/45	100.2°	14,900	32	23	3	42	28
6/19/45	99.6°	14,700	42	21	2	35	
6/26/45	98.4°	9,450	42	32	2	24	
7/ 3/45	98.8°	11,000	57	29	5	9	10

A biopsy of the gastrocnemius muscle was done with regard to the possible presence of trichinosis or periarteritis nodosa. This was reported as negative. No significant pathologic changes were seen in the blood vessels. There was no significant leukocytic infiltration. This patient continued to improve subjectively. Formerly she would cough on deep breathing for examination but this ceased. Temperature, which had remained slightly elevated, spiking to 100.6° F. daily, gradually came down on the twelfth hospital day and remained normal after the sixteenth hospital day.

On the seventeenth hospital day a chest film (figure 5) showed the small areas of density previously noted in the lateral portion of the lower right lung field to have practically disappeared, and there were now only dense perivascular markings. On the left side, the patchy density in the middle third of the lung had largely disappeared. There was still some fine mottling. The basal third of the lung was hazier than before and showed some slight mottling with thickened markings suggesting a development in this area of a pneumonitis not present before. On the twentieth hospital day a reëxamination of the chest including the examination of the esophagus with opaque mixtures showed no compression or alteration in the position of the esophagus. The areas of density in the right lung and left mid-lung field had largely disappeared, but there was still an area of increased density at the left base which represented an extension of the process. The hilar shadow and perivascular markings were accentuated on both sides and there was a dense sharply demarcated shadow just above the right hilum with a convex outer border which was consistent with an enlarged peritracheal lymph node. There was no evidence of free effusion in the pleural cavities.

On the twenty-fourth hospital day the patient was greatly improved and had practically no irritation in her trachea on breathing. She was up and about and climbing stairs. The eosinophilia was subsiding and her temperature was essentially normal. There were no signs in her chest on physical examination.

On the twenty-sixth hospital day chest reëxamination, in comparison with the film of June 29, 1946, revealed the right lung field was now clear with no signs of parenchymal disease. On the left side the dense area previously seen at the base largely absorbed. The left diaphragm was now seen fairly distinctly. An electrocardiogram taken on the patient showed, except for somewhat low voltage throughout, a normal record. The patient was discharged on the thirty-first hospital day as improved.

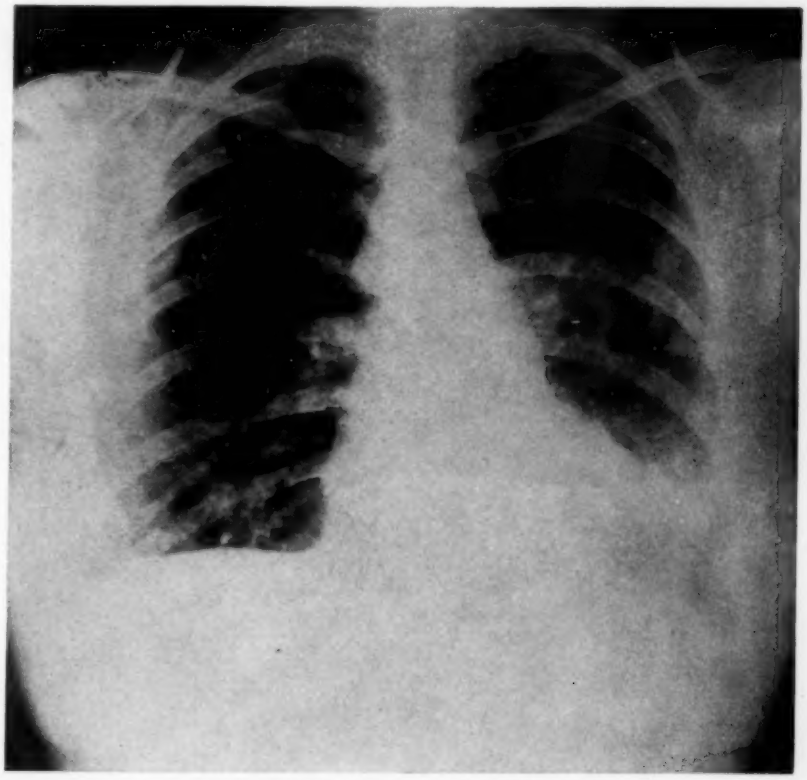

FIG. 5. Chest x-ray in Case 2 on seventeenth hospital day. It showed the patchy density of the middle third of the left lung to have largely disappeared. The left basal third of the lung was hazier than before suggesting a development of pneumonitis not present previously.

Case 3. H. S., a 27 year old white male veteran, was admitted to the hospital for the first time September 23, 1946 with the chief complaint of a chronic, slightly productive cough. The patient was well in all respects until August 1945, when in Paris, France, he contracted a cold from which was derived a chronic hacking, at times productive cough. The next month, September, he was separated from the service and returned to his home in Texas. However, the chronic cough persisted, sometimes better and sometimes worse. For the next 11 months until August 1946,

it became associated with sharp pains in his right chest and periodic fever. The cough was productive of a moderate amount of greenish, mucoid phlegm, never associated with hemoptysis. On September 21, 1946 he was seen by his family physician and a chest roentgenogram revealed some infiltration in the right lung. Hospitalization was advised.

Past History. Except for his Army service the patient had lived on farms. He had never worked in mines or quarries. As a child he had had the usual diseases,

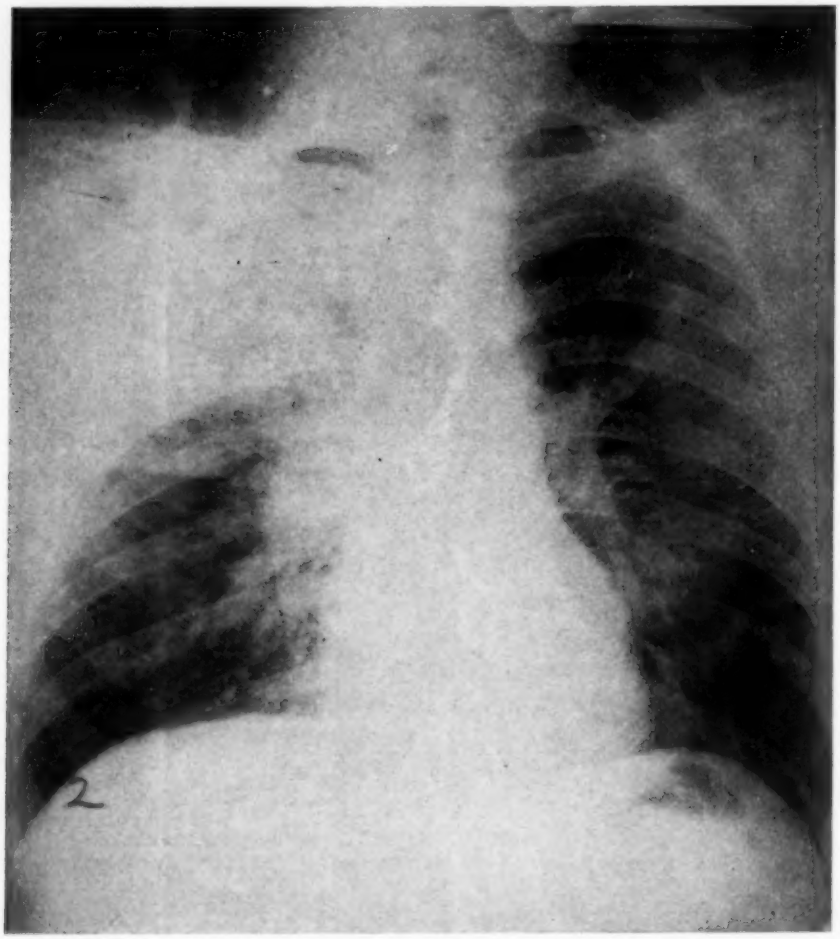

FIG. 6. Chest roentgenogram in Case 3 on September 23. It revealed almost complete consolidation of the right upper lobe.

all mild. Since the age of 18 years, he had suffered periodic attacks of hay fever when subjected to dust from corn and cornshucks. No other type of dust or allergies seemed to precipitate the hay fever. He had no history of asthma, migraine or urticaria. His battle service took him through North Africa, Sicily, Italy, Southern France, Austria and Germany. In 1942, while overseas, he was treated for acute gonorrhea with sulfadiazine with no residuals. He enjoyed excellent health until the last two months of his service.

Family History. The patient's father and one brother had had moderately severe asthma for many years. A sister suffered from moderate hay fever. There was no history of familial tuberculosis or known contacts.

Review of Systems. Non-contributory.

Physical examination was essentially negative at this time except for hypertrophied tonsils. Initial laboratory studies showed a normal urinalysis. Blood count revealed 11,000 white blood cells, 62 per cent neutrophiles, 22 per cent lymphocytes, 15 per cent eosinophiles, 1 per cent basophiles, hemoglobin 80 per cent; sedimentation rate (Westergren) 51 mm. in one hour. He was observed particularly for pulmonary tuberculosis, but repeated sputum examinations were negative for acid fast organisms. Chest roentgenograms were reported as follows: September 23 (figure 6). "Except for several small rounded areas of rarefaction there is almost complete consolidation of the right upper lobe. The lung fields are otherwise essentially clear." September 25. "There is a large area of infiltration involving the

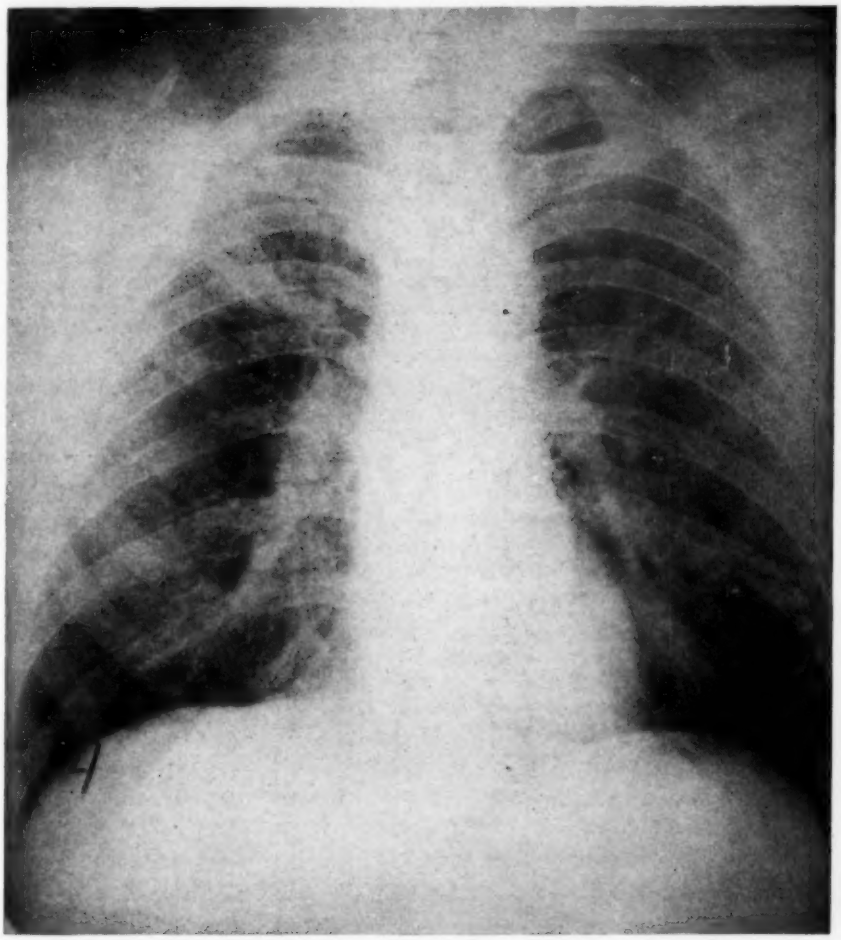

FIG. 7. Chest roentgenogram in Case 3 on October 7. It showed considerable resolution of previously described infiltration in the right upper lung field.

posterior segment of the right upper lobe, limited by the interlobar fissure between the upper and middle lobe. Within this area of infiltration several small translucencies are seen. The remaining lung fields are clear." October 2 (figure 7). "Reëxamination of the chest shows considerable resolution of the previously described infiltration in the right upper lung field. There is now only a small triangular area of infiltration in the periphery of the first costal interspace anteriorly. There is a small area of fibrosis in the second left costal interspace anteriorly extending from the hilum toward the periphery." October 7, 1946. "Reëxamination of the chest shows further resolution of the previously described infiltration in the right upper lobe posteriorly." October 21. "There is a slight increase in the amount of clearing over the previous examination. There is still a small zone of fibrosis at the level of the second rib anteriorly." October 31. "There is complete clearance of the previously described infiltration in the right upper lobe. No evidence of pulmonary tuberculosis." The patient was observed for 44 days and discharged with a diagnosis of resolved pneumonia. He was apparently well on November 6, 1946.

Second Hospital Admission (December 17, 1946).

The patient was admitted to the ENT Service for a tonsillectomy. After his last discharge he had felt well for a while but then began to have frequent sore throats and fever. A routine chest roentgenogram (figure 8) was taken and this was reported as "showing a fairly large area of consolidation in the second and third left costal interspaces anteriorly near the periphery. There is also infiltration in the left lower lung field near the left cardiac border. The right lung is clear." Tonsillectomy was postponed and the patient was transferred to a medical ward. At this time his only complaints were chronic cough, productive of small amounts of tenacious, mucoid sputum, and chest pains in the right mid-chest and lower left chest, described as sharp, catchy-like, related to respirations.

Physical examination at this time showed only hypertrophied tonsils. At times during his hospital stay occasional râles were heard in the left upper lung field without change in fremitus or resonance. His temperature remained normal except for three episodes of low grade fever. Initial laboratory studies showed a red blood cell count of 4,460,000, hemoglobin 90 per cent; white blood cells, 19,900 with 59 per cent neutrophiles, 11 per cent eosinophiles, 25 per cent lymphocytes, 5 per cent monocytes (table 3). On following examinations, the eosinophilia was reported as 29 per cent,

TABLE III

Summary of Data

Date	Temperature F.	White Cell Count	Neutrophiles %	Differential Count		Eosinophiles %	Sedimentation Rate mm. per hour
				Lymphocytes %	Monocytes %		
9/23/46	99.6°	11,000	62	22	1	15	51
12/18/46	98.6°	11,900	59	25	5	11	
1/ 2/47	99.2°	9,600	38	29		33	20
1/ 6/47	99.0°	8,300	38	40		22	
1/ 8/47	99.0°	11,000	38	20		42	
1/ 9/47	98.6°	8,000	26	39		35	
1/15/47	99.8°	8,200	40	30	2	28	10
2/ 3/47	98.6°	10,250	55	35	1	9	

22 per cent, 42 per cent, 35 per cent, 28 per cent, 9 per cent. Other blood studies were normal. Repeated urinalyses were negative. Sputum cultures and smears for acid-fast organisms were negative. Smears showed numerous eosinophiles. The feces were negative for ova and parasites. Tuberculin skin test was negative, as

were skin tests for trichinosis and coccidioidomycosis. Roentgen-ray reports (December 30, 1946). "There has been marked clearing of the consolidation in the left upper lung field. The infiltration in the lower lung fields is still demonstrable and the right upper lobe shows a residual increase in the pulmonary markings." January 6, 1947. "The left lung field is now essentially clear. There is a recurrent area of infiltration in the inner zone of the first right costal interspace anteriorly consistent with recent pneumonitis." January 14, 1947. "There is a small residual area of

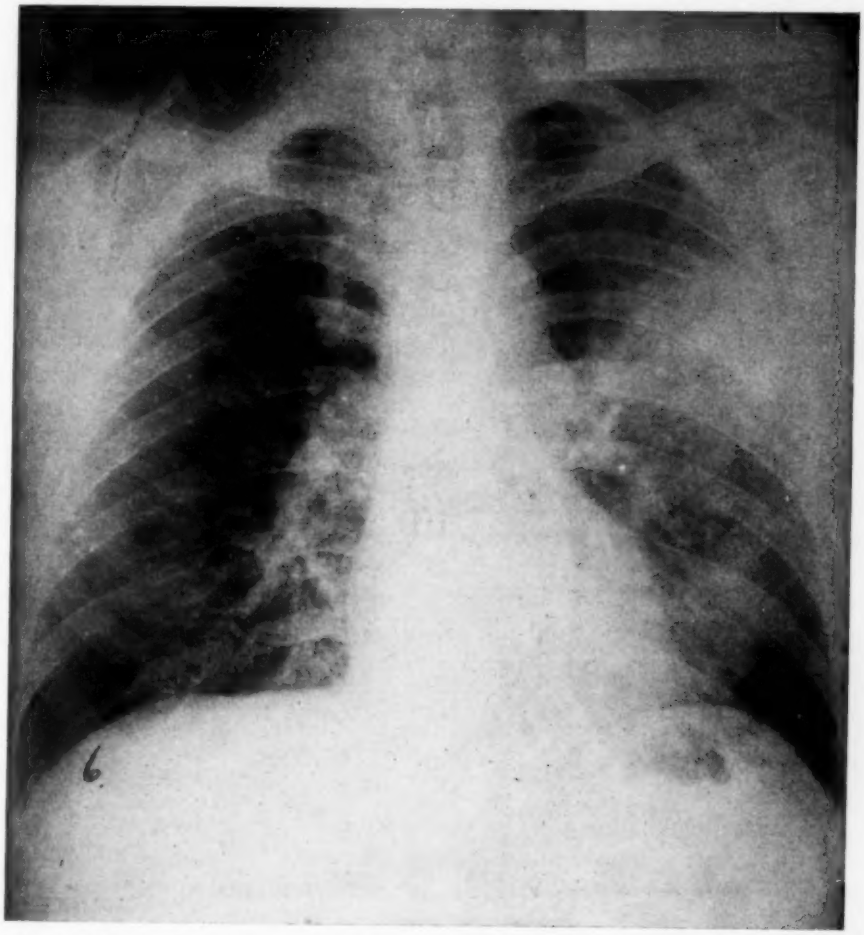

FIG. 8. Chest roentgenogram in Case 3 on second admission, December 17. It showed a fairly large area of consolidation in the second and third left costal interspaces anteriorly near the periphery. There was also infiltration in the left lower lung field near the left cardiac border. The right lung was clear.

infiltration in the right subapical region near the inner zone and another fairly round area of infiltration in the right lower lung field." February 14, 1947. "Reëxamination of the chest shows both lung fields to be clear except for a linear area of increased density in the inner zone of the right apical region." The common agglutination tests were all normal. On February 10 the patient underwent an uneventful tonsillectomy and was discharged as improved February 20. After his discharge he remained free from symptoms except for mild hacking cough.

Discussion

Case 1 presented a very unusual clinical course, and review of the literature has not revealed any similar case report. The onset of illness, on her first admission, was rather sudden, with physical findings minimal compared to the roentgenographic findings. She became very ill but her clinical picture did not resemble that of a true infectious pneumonia. Her skin was cool and moist. She had an expiratory grunt and tachypnea with short shallow respirations. Her white count rose as high as 31,950 with an eosinophilia of 41 per cent. The course was unusually stormy and she showed no response to sulfonamide therapy. It is interesting to note that on April 14 she received intravenous aminophylline and her pulse, temperature and respirations were within normal limits again for a few days. She developed a dry, hacking, non-productive cough, and her periods of intense cyanosis and apnea responded dramatically to intravenous aminophylline. Her blood, urine, and sputum cultures were consistently reported sterile. The stools were negative for ova and parasites. A skin test for trichinosis was negative. She had no previous allergic history but both her brother and sister gave a history of seasonal hay fever. On discharge her chest plate was clear and repeated check-up showed no recurrences of infiltration.

On her third admission, 18 months later, she developed a picture of tracheobronchitis. Again her chest and roentgenograms showed changing areas of density. She showed no response to penicillin therapy. Her highest eosinophilia was 4 per cent during this admission. It was the opinion of the roentgenologist that roentgenographic findings on the first admission resembled an interstitial pneumonitis, whereas on her third admission they were more consistent with an atypical pneumonia. This corresponded with her clinical picture.

The second patient ran a more benign course. She developed an irritating cough and ran a slight fever of 100 to 101.2° F. for 17 days. The chest never revealed any abnormal physical findings but roentgenograms showed changing shadows. Her eosinophilia reached 42 per cent. All tests for acid fast infection, ova and parasites, allergens, trichinosis, and periarteritis nodosa were negative. We felt that her symptomatology was too severe and the duration of her illness too great to represent a true Loeffler's syndrome. It is interesting to note that her onset resembled angina pectoris.

Our third case had a rather prolonged course with two episodes of pulmonary infiltration and eosinophilia. This patient had a positive family history for allergy and he himself had hay fever. Unfortunately skin tests were not done. All other tests were again negative as in first two patients.

As has been mentioned, the cause for this syndrome is not known, although hypersensitivity is suspected from its frequent association with vasomotor rhinitis and asthma. Various substances have been considered allergens in causing pulmonary infiltrations with eosinophilia.

Miller et al.[9] reported on a syndrome which they called allergic bronchopneumonia. Eleven cases were presented, most of whom had a positive allergic history. In describing the clinical picture they define it as a pneumonia or bronchial process in an allergic individual characterized by signs and symptoms indicative of bronchial obstruction and pulmonary infiltration with or without fever. The etiology or the predisposing cause is an underlying allergic constitution. Unlike true infectious pneumonia, the skin is usually cold and moist and pleuritic pain is conspicuous by its absence. The degree of cyanosis is variable. Examination of the nose shows boggy, purplish-white mucous membrane, and smears of nasal secretions will reveal numerous eosinophiles. The course may be shortened by administration of epinephrine which may produce a sudden cessation of symptoms and initial drop in temperature. Complications are rare. Death occurred in only one case. The causes mentioned were allergic shock, extensive allergic pneumonia, massive atelectasis or spontaneous pneumothorax.

Engel [10] described a similar clinical picture of pulmonary infiltration and blood eosinophilia in himself and a friend, and attributed the condition to hypersensitivity to the pollen of the privet plant. He considered bronchial asthma, atelectasis and traumatic origin, but found no confirmatory evidence.

Smith [6] presented a case of pulmonary infiltration with eosinophilia of 69 per cent in a 55 year old patient with previous history of severe bronchitis and asthma. Roentgenographic findings persisted from June 6 to July 18.

Baer [11] reported another case in a 30 year old asthmatic with lung infiltration and eosinophilia of 25 per cent. The infiltration shown by roentgenray was present from December 27 to January 6.

Karan and Singer [12] reported five cases of extensive pulmonary infiltration which roentgenographically simulated pneumonic tuberculosis. In two of these cases, there was eosinophilia of 9 and 15 per cent respectively. One had had attacks suggestive of mild asthma for many years; the other had an attack, during the course of illness, which was diagnosed as asthma by the referring physician. They were treated with adrenalin with some relief. The authors compared these cases to Loeffler's syndrome but stated that they differed in some respects from this condition, e.g., the symptoms were more persistent and pronounced, pulmonary infiltration was less rapid in clearing, and in one there was evidence of cardiac strain which subsided when the pulmonic condition subsided. It appears to us that when these two cases are compared with their other three and reported cases of atypical pneumonia of unknown etiology, so-called virus pneumonia, there are marked similarities. Differential points are eosinophilia and evidence suggestive of asthma. This suggests that these are instances of similar diseases occurring in allergic individuals. Whether the disease occurring in an hypersensitive individual merely stimulates the production of the eosinophiles on a non-specific basis, or whether the individual actually becomes hypersensitive to his new infection must be left to speculation. The condition occurs frequently enough

without asthmatic or other usual hypersensitive manifestations to warrant the consideration of the latter cause of eosinophilia.

Weingarten [13] described a disease entity peculiar to India beginning with lassitude, fever of 100 to 101° F. in the evening, loss of weight, development of a dry, hacking cough, and development in about a week of expiratory dyspnea lasting several weeks. It was often accompanied by considerable wheezing and some cases had severe attacks of typical bronchial asthma occurring regularly at night. Physical signs included sibilant and sonorous rhonchi and prolonged respirations. Sputum was absent or scarce, tanacious and glassy. Splenomegaly three to five centimeters below the costal margin was present. The eosinophilia was striking, going as high as 88 per cent. Roentgenographic examination showed nonconfluent disseminated mottling of both lungs.

Peirce and his associates [14] described several cases with blood eosinophilia and focal pulmonary edema. Six of the eight cases had definite history of asthma or some specific hypersensitivity. The authors believed that the roentgenographic evidence strongly suggested that this variation from the normal was probably due to interstitial edema rather than to the cellular infiltrate of an infection. Consideration of "transient focal pulmonary edema" was suggested as the probable pathophysiologic process, perhaps as one of the manifestations of allergy.

In 1944 Peabody,[15] in citing the paucity of cases in the American literature, said: "My own search of the American and English literature has revealed considerably fewer than 25 cases, even if all reported cases should be accepted as authentic." He reported a patient who had chronic "asthma" and who was hospitalized three times with asthmatic attacks, fever, pulmonary involvement and high eosinophilia. On one occasion the entire left lung field was occupied by an extensive infiltrative process and possible cavity. Four months later the lung fields were clear. We feel that this patient's manifestations were too severe for a true Loeffler's syndrome.

In 1933 Cole and Korns [16] recorded an instance of recurrent pulmonary involvement associated with angioneurotic edema and high eosinophilia. Serra [17] mentioned that except for the fact that this patient died the case had some resemblance to the syndrome.

Bagenstoss and his associates [18] reported a case in a woman aged 59 with "symptomatic nonspasmodic 'asthma' of seven years' duration." She complained of severe cough, breathlessness and anorexia. Roentgenograms of the chest showed infiltrations which apparently lasted from June 24, 1944 to her discharge September 11, 1944. On December 31 she suddenly became ill with substernal discomfort and severe, progressive dyspnea and died five days later. At autopsy there were large numbers of eosinophiles in the pneumonic exudate and granulomatous and fibrous changes with necrotic arteritis and phlebitis of the allergic type. The authors present this as a case showing the outstanding histological features of pulmonary lesions in

a case of Loeffler's syndrome. They suggested also that the picture appeared quite similar to the changes observed in periarteritis nodosa.

Müller,[19] also quoted by Schultze,[20] considered that the pulmonary infiltrations associated with eosinophilia and described by Loeffler were a result of ascaris infiltration although the ascaris frequently were not demonstrable in the sputum or in the stools. He cited as evidence the following occurrences. In January and February of 1938, four physicians including himself developed the typical clinical picture after the repeated eating of young cress that had been grown in a greenhouse. It had been fertilized by manure from pig and horse stables. Ascaris larvae could not be demonstrated in the sputum at the time nor could young worms be found in the stools later. As final proof of the causes of these cases he took by mouth three teaspoonfuls of the soil in question. After the expected incubation period of eight days, the typical symptoms complex developed and lasted the usual length of time, with multiple shifting lung infiltrations, mild degree of illness, eosinophilia up to 19 per cent, and leukocytosis. Unfortunately no mention was made of any attempt to recover ascaris forms from the soil ingested.

Loeffler [2] cites the work of Koino [21] who showed ascaris eggs in the stool either before, during or after the onset of the pulmonary infiltration. Koino showed that ascaris larvae in their wandering can cause pneumonia—highly febrile, clinically severe with hemorrhagic sputum in which from five to 10 days ascaris larvae in great numbers can be demonstrated. This was experimental, Koino having swallowed 2000 ripe fertilized eggs.

Other parasites and ova have been associated with eosinophilia and pulmonary infiltration. Stephano [22] reported a case that had amebae in the sputum but not in the stool, and both the lung infiltration and accompanying asthma disappeared after emetine therapy.

Hoff and Hicks [5] reported one case in which symptoms and roentgenographic findings persisted for four months until amebae were eliminated from the stool. The patient showed dramatic response to emetine therapy. Lavier, Bariety and Caroli [23] have reported this syndrome in a case of infestation with *Fasciola hepatica.* Miller [4] reported a case with a maximum of 85 per cent eosinophilia. Ova of *Trichuris trichiura* were found in the stools. These disappeared on antihelminthic treatment but the clinical course was unaffected. The patient also received mapharsen therapy and improved.

Wright and Gold [24] observed nine cases of cutaneous helminthiasis with associated pulmonary infiltrations and peripheral eosinophilia. The authors stated that "When erroneous diagnosis or procrastination in therapy of the local skin lesions occurred, the pulmonary infiltrations continued a migratory course over a period of weeks."

Scherlis [25] presented one case with a benign course with roentgenographic findings on November 19 and November 23, which had cleared by November 27. Jones and Souders [7] reported a case in a 33 year old negress in whom

the illness was mild. Roentgenographic findings in the chest were present from October 21, with complete disappearance by December 7.

In 1939 Smith and Alexander [26] presented a fatal case of so-called "Loeffler's syndrome" in a seven year old girl. The girl had bronchopneumonia in September with a relapse in October. Examination showed malnutrition, bronchitis, anemia, white blood count 31,000 with 39 per cent eosinophilia, a spiking temperature to 104.5° F., bilateral transient miliary infiltration; the peak eosinophilia at 10 days was 54 per cent. She had a long stormy course. Postmortem examination showed hemorrhagic and necrotic areas in the lungs. Although leukemia seemed likely, no definite diagnosis was made. The whole picture did not fit a true Loeffler's syndrome.

Serra [17] presented a case in which there were four separate attacks over a period of 32 months. The fourth attack was of 26 months' duration at the time of the article's appearance. The etiologic factor could not be determined but the occurrence of hives, eczema and eosinophilia supported hypersensitivity as a basic factor.

In 1942 Elsom and Ingelfinger [27] reported two cases of pulmonary infiltration accompanied by an eosinophilia and definite evidence of brucellosis in both cases.

Coccidioidomycosis must also be considered, since it is primarily and predominantly a pulmonary disease and is associated with various roentgenographic findings and eosinophilia up to 89 per cent.[28, 29, 30]

Comment

Since Loeffler's original article,[1] there has been much written and said about Loeffler's syndrome. With the present tendency to pigeon-hole every disease under a definite name, a great many conditions with superficial resemblance to Loeffler's syndrome have come to be described under that name. This seems rather unfortunate in that it tends to cloud the matter in a veil of uncertainty and to imply that it is a disease with varied clinical manifestations and definite etiology, rather than a restricted symptom complex of unknown and possibly varied etiology. Loeffler's syndrome is a distinct entity characterized by migratory and at times recurrent benign pulmonary infiltrations.

Müller [19] has given the most suggestive evidence that there may be a specific organism that causes the symptom complex, although he was unable to demonstrate the organism, nor did he give any evidence that different organisms might not produce the same effect.

Most of the other cases of pulmonary infiltration with eosinophilia that we have found in the literature in this country do not conform strictly to the syndrome described by Loeffler. It seems possible that they may be variants of the same pathological process which is produced by the same or by somewhat similar etiological agents, such as parasitic worms. With few exceptions, notable in the cases of Jones and Souders,[7] Baer,[11] and Scherlis,[25] the

illness was too severe or the signs of too long duration to warrant, it seems to us, labelling them Loeffler's syndrome.

Serra [17] mentioned that this disease is reported under many different titles with Loeffler's syndrome added in parentheses. He suggested the term "Benign pulmonary infiltrate" to allow for the inclusion of possible cases without eosinophilia, as well as those of longer duration than usual. We feel that the cases which fit into the initial symptom complex should be called Loeffler's syndrome but suggest that all other cases be termed pulmonary infiltration with blood eosinophilia associated with an unknown or known etiological factor.

In general, there has been a tendency to associate with Loeffler's syndrome any case with pulmonary infiltration and eosinophilia. This combination of pulmonary infiltration and eosinophilia may appear in any age group, from infancy to old age. It may be associated with a benign and mild clinical picture, as in true Loeffler's syndrome, but in some cases the course has been very stormy, as illustrated by Smith and Alexander's case and by our first case, whereas our second and third cases showed a less severe, but quite protracted course. It has occurred in association with definite asthmatic tendencies or other specific allergies, with *Endameba histolytica* infection and other parasites such as *Fasciola hepatica, Ascaris lumbricoides,* and trichinosis,[31] with cutaneous helminthiasis and with brucellosis. In many cases no specific etiological factor or agent has been demonstrated. It is an unusual response of the body tissues which is occasionally seen in many different conditions, with or without the manifestations generally considered to be hypersensitive in nature.

Search for the etiological agent is important in each case. In one instance, there may be a specific allergen to which the patient is sensitive or there may be a parasitic infestation which will respond to specific therapy. These may be found only by thorough study of the history, clinical findings, and laboratory investigations. As Miller [4] pointed out, periarteritis nodosa, Hodgkin's disease, and eosinophilic leukemia must be considered in the differential diagnosis, but usually can be ruled out by the clinical course. Familial eosinophilia could not be ruled out in his case. Pulmonary tuberculosis must be considered, and the patient followed carefully.

In case of an allergic background or a stormy course, it must be borne in mind that adrenalin or aminophylline may alleviate the course. In our first case, it appeared that the patient would have died had it not been for the administration of aminophylline intravenously. Miller and his associates [9] found epinephrine useful in their reported cases of allergic bronchopneumonia.

Summary

1. Three cases of pulmonary infiltration with blood eosinophilia are reported.

2. The first case had a long, stormy course which did not resemble the typical Loeffler's syndrome. The second case had a less severe but quite protracted course with onset suggesting angina pectoris. The third had a prolonged course with two episodes, and of the three cases it was the only one with a definite hypersensitive background.

3. In none of the cases was an etiological agent found.

4. Various conditions in which pulmonary infiltration and blood eosinophilia are associated have been reviewed.

5. The importance of searching for an etiological agent and giving specific therapy when indicated is emphasized.

6. A plea for a more useful and standard nomenclature is made.

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OBESITY AND ITS TREATMENT, WITH PARTICULAR REFERENCE TO THE USE OF ANOREXIGENIC COMPOUNDS *

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In spite of the frequent enlightening discussions in social and scientific circles on factors contributing to the development of obesity and on the treatment of this condition, there continues to be a vast number of markedly obese individuals. The deleterious effects produced by this condition, directly or indirectly, are much greater than seems to be generally recognized. In addition to the social and occupational handicaps and associated mental distress which obesity causes, it predisposes to the development of cardiovascular diseases and diabetes mellitus. Marked obesity exerts a pronounced effect on life expectancy. For example, Dublin and Lotka [1] found that individuals aged 45 to 50 with excess weight of 50 pounds had a 56 per cent increase in death rate, and the ones with an excess of 90 pounds had a 116 per cent increase.

For several years we have followed a number of obese patients in the Endocrine Clinic of the Boston City Hospital. In treating these individuals we explained the disease to the patient as being one of a positive calorie balance and we attempted to point out certain factors which modified this balance. We endeavored to treat the obesity chiefly by restricting the food intake to from 400 to 1200 calories per day and by correcting some of the factors which contributed to the obesity. Occasionally desiccated thyroid was used as an adjunctive therapy, and more often "Benzedrine" was prescribed. This regimen proved to be satisfactory in many patients, but many others were seen from year to year in more or less the same markedly obese state, in spite of the many prolonged "sermons" which had been "preached." These failures in therapy were due largely to the patient's inadequate willpower to execute the prescribed regimen. Consequently, we chose to decrease the desire for food by administering anorexigenic compounds of a type similar to "Benzedrine." The latter drug had proved to be unsatisfactory in many patients because of certain undesirable symptoms which it produced. Therefore, several compounds were studied in the hope of ob-

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taining ones which had pronounced anorexigenic effects without other undesirable actions.

Before describing the studies with these drugs, factors contributing to obesity are discussed because drug therapy should be considered only as an adjunctive therapeutic measure. As will be indicated later, the chief effect of the compounds used was to decrease the total amount of food ingested. In cases where an adequate restriction of food intake can be voluntarily induced, there is no need to prescribe the anorexigenic compounds. Moreover, it is important to correct as many of the factors contributing to obesity as possible, whether or not specific drug therapy is given.

Consideration of Factors Contributing to Obesity

A lengthy discussion of the factors considered by various investigators as contributing to obesity is not given in this paper, since there have been many reviews on the subject, among which may be mentioned those by Newburgh [2] and Evans.[3] Many of the comments which we make are not original, but seem to warrant repetition because of the frequent use of unsatisfactory therapy in obesity.

It is clear that obesity results from the ingestion of more food than is utilized. However, there are a vast number of factors which may influence this balance and it is often advisable to attempt to correct them as much as possible. We like to obtain the patient's opinion as to the cause of his obesity. Although his ideas may be inaccurate, they often afford the basis for peculiar behavior, dietary or otherwise.

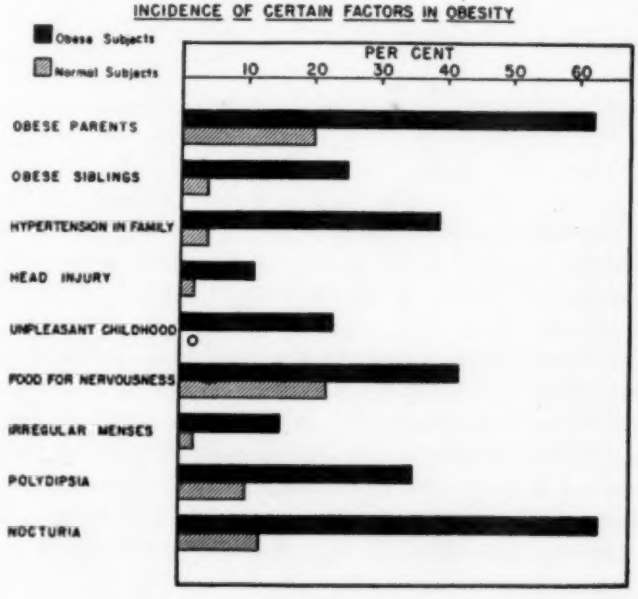

Fig. 1.

Ninety-six markedly obese subjects, chiefly nurses, were studied carefully with reference to their family background, environment, development, general eating habits and physical status. For comparison, 50 non-obese individuals were selected with reference to occupation, social and economic status, age and sex. The tabulations of the observations in these groups of individuals are in accord with the conclusions drawn from experience with much larger series of patients followed in this clinic.

Only 12 per cent of the patients were of the impression that "glandular disease" was primarily responsible for their obesity. Seventy-eight per cent stated that overeating had caused their excess weight and listed a variety of factors, discussed later, which contributed to this. The other 10 per cent admitted that they did not have a good concept of the factors causing obesity.

1. *Family Influences.* As may be observed in figure 1, obesity occurred much more frequently among the parents and siblings of obese patients than of normal individuals. Wilder [4] suggested that in some instances of familial obesity there might be an increased activity of the centers of the diencephalon controlling feelings of hunger and satiety. The exposure to the same environment and habits is doubtless important in family obesity. Twenty-three per cent of the patients, compared with 12 per cent of the controls, stated that their family tended to eat excessively. In some families the caloric requirements of certain members were much higher than for others, but the same bountiful servings were given for each, and the child was punished if he did not "clean the plate."

TABLE I

Age at Which Patient Considers That He First Became Definitely Obese

Years	Per Cent
0–10	16
10–20	21
20–30	27
30–40	27
40–49	9

As shown in table 1, only 37 per cent of the subjects considered that they were obese before the age of 20; however, in many instances it was the continuation of family habits of overeating which led to the development or increase of obesity.

2. *Emotional Influences.* Perhaps the most underrated cause of obesity is the soothing effect of eating upon certain emotional tensions as well as upon a general state of nervousness. Some patients stated that when they were restless, lonesome or bored they obtained some relief by eating. Others were so comforted during feelings of abuse, whether caused by episodes of disappointment or misfortunes in life, or physical defects. A feeling of unpopularity among friends and relatives was particularly conducive to hyperphagia. Sometimes this mechanism of compensation for maladjustments was instituted more by the parents than by the patient.

On the other hand, some patients in their desire "to be sociable" ate more food than they knew was required, as illustrated by the following comments made by a highly intelligent and well-informed patient. "It is impossible to diet and eat with normal individuals who are on regular diets. All social activities of life center around either eating or drinking and no one is really conscious of this until he or she gets on a diet; then there is a constant barrage of invitations to dinners, to tea, to cocktail parties, to go off for the week-end, or play bridge and be served refreshments—even to drink a Coca Cola, which has 80 calories. Often one ponders what more life could offer to a thin person than to a fat one, and the only answer is more years to enjoy it." In this patient is illustrated the important rôle of her philosophy upon her state of obesity. This individual is acquainted with most of the known pertinent facts about obesity and can choose her course. However, there are many individuals who eat excessively "to be sociable," but do not realize that marked obesity may result ultimately and may interfere greatly with their social standing and general happiness. It is perhaps the final realization of this situation that partly accounts for the higher incidence of suicides [5] in obese individuals than in non-obese ones. Fifty-one per cent of our patients stated that they were nervous or "high-strung." Many said that "inwardly" they were nervous.

The state of unhappiness often came on gradually over an interval of many years and was intensified as part of a vicious cycle that could be avoided. For example, Mrs. B., aged 46, and her husband were each slightly overweight at the time of their marriage 20 years previously. Mr. B. was very popular and his interest in civic activities frequently kept him away from home at night. Upon these occasions Mrs. B. usually attended a movie. She generally went alone since it was too troublesome to get someone to go with her. She would feel lonely when she got home because it was usually an hour or more before her husband arrived. During this time she ate various things "even though I was really not hungry, but because I received a reimbursement in food of what I lacked in other pleasures. It allayed some of my nervousness and gave me something to do." As the years passed and her weight increased greatly she found that the climb up the high hill from the movies to her home was strenuous exertion, so she began going home in a taxi-cab. Soon the pleasure derived from the movies did not seem to justify the expense involved so she just stayed at home and "nibbled at food." As her weight neared and passed 300 pounds she became ashamed to appear in public and felt that her husband was ashamed of her. Moreover, her husband's relatives were quite critical of her slovenly state. These factors made the patient feel all the more sorry for herself and more nervous; as a consequence she ate more. She finally became very high-strung and believed that there was nothing in life for her but misery. In treating this patient we not only helped her to lose more than 100 pounds, but assisted her in planning activities which would contribute to the betterment of her community and her family. She gained so much pleasure from

this type of work that she no longer had to depend upon eating for her pleasures.

The following statements made by one patient illustrate a not-uncommon problem in obesity. "Early in life I think that old-fashioned doctors, over-indulgent parents, etc., thought that a chubby baby was pretty and healthy, so nothing was done to control my diet. As I grew up, fat, awkward and bespectacled, I was too unhappy to do anything beyond feel sorry for myself. My sister was pretty and slim and I was jealous."

Another patient made these comments: "I believe that most people are obese because of improper eating habits. People who are obese eat, not, I am certain, from a need of food, but for the sensual pleasure derived from flavors which are pleasant to them. I, also, eat long after I am full because I enjoy food flavors. I consider this a form of infantile greed. Occasionally, I find myself restless enough so that I am unable to divert myself by reading, etc. At such times I usually eat."

The comments made by the aforementioned patients, as well as ones made by others, indicate that many of the patients had a good insight into some of their dietary troubles.

3. *Eating Habits.* Many patients related that they ate most of their food at night. They stated that they ate little or no breakfast and a light lunch, but ate a "good" evening meal and continued to eat "off and on" until bed time. Some of the patients had so little desire for breakfast that it was difficult to make them eat this meal. The reasoning of many of these subjects was: "Since I have eaten essentially nothing at two-thirds of the meal times, there does not need to be much restriction during the other times."

When 96 patients were questioned concerning the three articles of diet which did most to cause their obesity, sweets, bread, and potatoes were listed far more frequently than were any of the others. However, there were distinct individual variations. Whereas some subjects stated that they had a very strong desire to eat a pound of candy at once, others stated that they had absolutely no desire for candy and had eaten none for many months. Certain patients ate large quantities of butter, mayonnaise, gravy, etc., while others had very little desire for them. Many subjects were of the impression that the excessive ingestion of water played a significant part in the development of their obesity. Thirty-five patients believed that they drank distinctly more water than did normal individuals. This characteristic was probably the main factor accounting for the nocturia which 63 per cent of them experienced.

Many patients stated that they did not eat very much food, but calculation of the caloric intake showed that they were consuming much larger quantities than they had realized. Not infrequently there was a marked misconception of the relative caloric value of foods. In some instances the volume of food was relatively small, but it was rich in calories. Moreover, the amount that they were eating between meals was often much greater than they appreciated. Overeating was spasmodic in some patients. They restricted their

eating for several days and then went on an "eating splurge" for one or two days.

4. *Metabolic Rate.* The law of conservation of energy must be respected in correlating the number of calories ingested with the deposition of adipose tissue. The body metabolizes enough food to supply the amount of energy required. When an excess of this energy source is ingested it is stored as carbohydrate, protein and, especially, as fat. Markedly obese subjects generally metabolize more food when in a basal state than do normal individuals, but when the oxygen consumption is expressed in terms of the surface area of the body, there is no significant difference in the two groups. Thus, the basal metabolic rate of obese patients tends to be normal. However, the rate of metabolism fluctuates markedly throughout the 24 hours of the day in accordance with various activities, especially the amount of physical exertion and the emotional reactions.* In a number of our subjects who became obese the daily activities were generally less than normal, although they did not eat any more food than did normal individuals. Earlier needs for a large intake of calories, as for example in athletes, were often not followed by a reduction in food when a sedentary existence was assumed, the individual having continued to eat until the previous sensations of fullness and satiety were obtained.

5. *Question of Dysfunction in the Assimilation and Metabolism of Food.* A question that still arises in the minds of many patients and some physicians is whether obesity results from a qualitative alteration in the manner of handling food in the body. Much evidence has been accumulated [2, 3] to indicate that obese individuals (a) do not have greater efficiency in digestion, (b) do not absorb a greater proportion of ingested food than do normal subjects, and (c) do not have a qualitative defect in the storage and utilization of fat, nor in the conversion of carbohydrate to fat.

6. *Injury to Hypothalamus.* Ranson and associates [6] showed that injury to a specific portion of the hypothalamus in rats led to the production of marked obesity. Brobeck and colleagues [7] demonstrated that in animals so treated the weight gain depended entirely upon the increase in food consumption; these rats used fats normally when fasting. Moreover, the oxygen consumption was the same as in normal animals of the same weight.

Eleven per cent of our obese subjects had had severe injuries to the head, as compared to two in the control group. One patient, aged 20, stated that she was slightly underweight until the age of 10, when she was hit by an automobile and received a fracture of the skull. On the day of injury she developed an insatiable desire for food and rapidly gained weight until she weighed 313 pounds. Another patient, aged 42, was underweight and of short stature until the age of 10, when she fell off of a ladder, landing on her feet. The following day she developed a pronounced hunger which persisted. Her weight increased to 270 pounds.

* Mentation is generally stated not to cause much oxygen consumption. However, when the nature of mentation is such as to provoke pronounced emotional reactions, the oxygen consumption may be increased enormously.

In the other patients receiving injuries there was not a definite association of hyperphagia with the injury.

7. Endocrinopathies. Endocrine abnormalities are often said to be the basis of obesity. However, the evidence indicates that endocrinopathies are rarely the cause of more than mild obesity. When obesity does occur in such cases it results chiefly from the imbalance of energy output and intake.

A. Clinical Studies

a. Pituitary. Individuals with hypopituitarism, unassociated with hypothalamic injury, usually are of normal or subnormal weight. Individuals with Froehlich's disease may be quite obese, but the primary injury in this entity is not in the pituitary gland. With hyperpituitarism, as with acromegaly or Cushing's disease, the subject rarely becomes more than slightly obese. Moreover, most obese subjects do not have the clinical picture of these endocrine diseases.

b. Thyroid. Hypofunction of the thyroid gland has often been designated as the cause of obesity, but much evidence has been produced to refute this view.[2] Estimation of the basal metabolic rate was made in 69 of our patients; in 61 the rate was found to be between −10 and +10 per cent. The values obtained in the other patients were −13, −15, −16, −17, −22, +11, +15, and +22 per cent. Eleven of 24 obese patients, unselected, were found to have less than 4 γ of protein-bound iodine per 100 c.c. of plasma,[8] but in view of the clinical picture, the essentially normal basal metabolic rates, the insignificant response to treatment with from 1 to 2 grains (U.S.P.) of desiccated thyroid daily, and the infrequency of significant obesity in myxedematous patients, thyroid deficiency does not seem to be a very significant cause of obesity.

A few patients with thyrotoxicosis and some obese subjects treated with desiccated thyroid gain weight, presumably as a result of the increased appetite.

c. Adrenals. Recent observations[9, 10] have indicated that certain of the adrenal steroids promote the accumulation of fat in the body. These studies are quite interesting, but more information is needed to ascertain whether these steroids are of significance in the etiology of the usual type of obesity.

Most patients with Cushing's disease are obese, but rarely is the obesity marked. The obesity in this disease is probably related partially to the excess amount of glucose available with supposedly an adequately supply of insulin. The peculiar configuration of the body is due partially to the loss of protein structure along with fat deposition and to postural changes. Moreover, the adiposity has a characteristic distribution in the body. Not many of the classical manifestations of Cushing's disease are present in the average patient with obesity.

Estimation of the 17-ketosteroid excretion in 18 markedly obese adult female patients, below the age of 55, showed a decreased excretion in 9

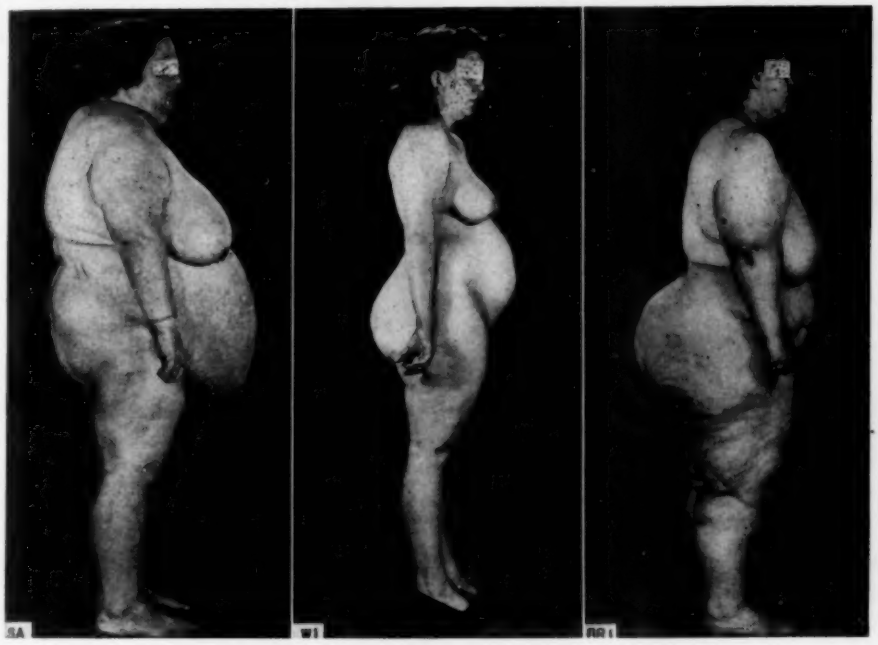

FIG. 2. Note the variation in distribution of fat.

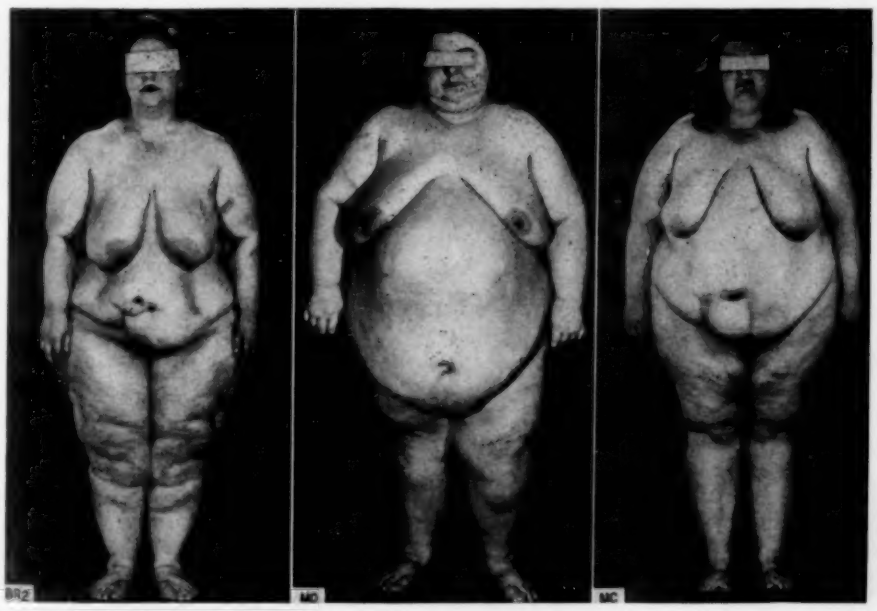

FIG. 3. Note distribution of fat. Patients BR and MC specifically related the onset of hyperorexia to cranial injury. Patient MO had become bed-ridden from her obesity.

(below 5 mg. per 24 hours) and an increased excretion in 1 (17 mg.). The "cortin" excretion was normal in each of 11 patients.

d. Gonads. Many hypogonadal individuals, male and female, are somewhat obese, but there are many others who have very little or no obesity. Although there is a tendency for obese patients to have secondarily decreased gonadal function, in most of the cases this is slight. Of the 34 married obese women whom we studied there was an average of three pregnancies.

e. Pancreas. Hyperinsulinism may produce hyperphagia and thus obesity, but this entity is rare.

B. Animal Studies

In a separate study [8] the amount of fat in the entire body of rats was estimated at intervals of from three to eight weeks after removal of the pituitary, thyroid, pancreas, adrenals, testes or ovaries, but the fat was found to be increased either very slightly or not at all. Moreover, the administration to normal rats, for intervals of more than three weeks, of thyrotropin, adrenotropin, pitressin, desiccated thyroid, cortin, adrenalin, lipocaic, insulin, progesterone, estradiol, diethylstilbestrol or testosterone did not cause significant increase in fat.

Fat Distribution in Patients

The distribution of fat varied a great deal, as indicated by figures 2 and 3 and table 2. It was amazing to observe how enormous accumulations of fat occurred in some regions, without there being much increase in other areas. In other patients, the relative quantities of fat in these sites were found to be reversed. In the markedly obese males most of the excess fat was in the abdomen and, to a lesser extent, on the chest. In addition to having a great deal of fat in these areas, the female patients often had marked accumulations in the gluteal region, hips, thighs and breasts.

The heights of the patients were of about normal average.

The blood pressure was more than 140 systolic and 90 diastolic in 20 of 130 patients. (Thirty-nine per cent of the obese subjects, compared with 4 per cent of the controls, stated that at least one of their parents or siblings had hypertension.)

Treatment

The preceding data have been presented in order to serve as a basis for rational therapy in obesity. Until shown contrariwise, it seems feasible to assume that ordinary obese subjects assimilate and metabolize their food in the same manner, qualitatively, as do normal individuals. It is clear that obesity develops because the fat and fat-precursors are ingested more rapidly than the fat is metabolized. There is a positive calorie balance involving fat, and to some extent, carbohydrates and proteins, since they contribute to the accumulation of fat. When the daily ingestion of calories is below the

Table II

Relative Increase in Amount of Fat in Certain Areas of the Body

TABLE II

Relative Increase in Amount of Fat in Certain Areas of the Body

* Males.

+ = slight excess; ++++++++ = massive amount of fat.

demands of the body for energy, the stores of carbohydrates, fats and proteins are, in order, preferentially metabolized. Therefore, in the treatment of obesity it is clear that a negative calorie balance must be produced and this can be accomplished only by reducing the energy intake (food) or by increasing the energy output.

A. *Therapy Causing Increased Expenditure of Energy.* The chief methods that have been proposed for increasing the energy output are the administration of (a) desiccated thyroid, (b) dinitrophenol, (c) stimulation of the central nervous system (atropine, caffeine, 2-aminopropanes, etc.), and (d) increased exercise. When effective in reducing weight, each of these methods usually produces hypermetabolism. Since many obese subjects are less energetic than the average non-obese individual, increased mental and physical activity are probably desirable in many patients. However, such is not desired in some individuals with cardiovascular disease and certain other complications. Much more exercise is needed to produce weight reduction than is often realized. Some of Newburgh's illustrations[2] make this very emphatic. For example, it is estimated that a patient weighing 250 pounds will have to climb 20 flights of stairs to expend the energy contained in one slice of bread and he must walk 26 miles to rid himself of 1 pound of adipose tissue!

When the good and bad effects are evaluated, these therapies are not generally very satisfactory, with the exception of certain aminopropane derivatives discussed later. Some patients lose a great deal of weight with desiccated thyroid therapy, when given in doses of approximately 3 grains daily. However, others may be bothered with headache, nervousness, dizziness and palpitation and may not lose much weight. We have seen several individuals who had taken desiccated thyroid with subminimal dietary requirements who developed Graves' disease and we consider that there is possibly a causal effect in these cases. Contrary to Evans' viewpoint,[3] we believe that desiccated thyroid offers more promise when given to children who are obese and have delayed puberty, even though they may have a normal basal metabolic rate. It is even more desirable if such adolescents are also of short stature. The beneficial effects of thyroid in this situation seem, however, to be due more to its augmentation of growth and maturation than directly to a hypermetabolic effect.

B. *Therapy Causing Decreased Intake of Calories.* Measures directed toward decreasing the caloric intake are more effective in treating obesity than are ones producing hypermetabolism. They have consisted of (a) the use of cathartics (decreasing the absorption of food), and (b) decreasing the ingestion of calories. The first of these measures is quite unsatisfactory. The latter is the most effective form of therapy, but usually necessitates far more than to tell the patient to "cut down on your sweets, potatoes, pastries, and butter," and necessitates more than to hand him a diet sheet with didactic instructions. The factors which contributed to the patient's obesity must be ascertained, explained to him and corrected. However, the patient may

not appreciate this aid until he has become convinced of the ill effects of marked obesity. He must know that this condition may interfere markedly with his social and economic attainments, his health, his life expectancy and his general happiness. Thus he must learn "the price of obesity." Moreover, he should become determined not only to lose the extra weight, but to prevent its recurrence. He should know that it will probably be necessary to observe certain precautions in eating for the rest of his life. Such convictions are necessary regardless of the type of therapy employed.

He should also be convinced early in the course of therapy that no matter how little he has been eating, or whatever contributory factors may have existed, his consumption of calories, in excess of his energy output, should be eliminated. Some of the facts that should be clarified in the patient's mind may be summarized as follows: (a) Overindulgence in food "just to be sociable" may ultimately defeat its own purpose, leading to a somewhat asocial state. (b) When obese subjects eat more food than they want and need, "just to clean the plate," they should visualize themselves as a greasy garbage can—the repulsive effect is desired. (c) Sensual pleasures leading to obesity should be replaced by habits less costly to health. (d) Excess eating as a mechanism of compensation for unhappiness should be corrected, if possible, by helping the patient to make satisfactory adjustments to his emotional distress. (e) The body requirements for energy vary greatly in different individuals and even in the same individual under varying circumstances, and the amount of food ingested must be adjusted accordingly. (f) Desire for non-fattening foods can be created. (g) The patient should become familiar with caloric content of food and should adhere to the regimen of eating, exercise, etc. prescribed. (h) *There are no magic drugs that can satisfactorily bring about weight loss in the face of continued ingestion of excessive food.*

1. *Instructions Concerning Diet.*

The caloric value of the diet of choice varies a great deal in different patients. Some patients follow a diet which is of very low caloric content better than one of moderate amount, because the greater weight loss associated with it makes it more "worth the effort." Strong and associates [11] found that diets of only about 400 calories daily could be given for several weeks, provided that one gram of protein per kilogram of ideal body weight and about 75 per cent of this amount of carbohydrate is given daily. All of the essential amino acids must be given. A diet of only moderate bulk is desired. It is wise that the patient learn the relative caloric value of foods and that he be permitted to have a wide field of selection, especially if he eats with many other people who do not restrict their calories. However, patients who are not very intelligent or who do not exercise their willpower very much are usually given less latitude in choosing the articles of diet. The patient should eat three meals a day, eating lean meat or fish, egg, milk,

fresh fruit and two vegetables daily. The vegetables should be chiefly in the "5 per cent" class. The patients with marked obesity should avoid sugar, potatoes, candy, pastries, fatty foods. Mineral oil may be used for frying. When diets of from 400 to 600 calories are used for several weeks we supplement them with vitamins A and D and the B-complex. For diet lists and detailed instructions the reader is referred elsewhere.[2, 3] A loss of from one to two pounds per week is perfectly satisfactory for most of the patients. In some of the tremendously obese subjects it is best to hospitalize them and then a reduction in weight of from three to five pounds per week can be produced.

2. *Anorexigenic Drug Treatment.*

In spite of spending a great deal of time in following the principles which we have presented thus far, we found that there was an appreciable number of obese patients who remained obese during intervals of several years. Of course, they had not completely followed the regimen prescribed. They failed to lose a significant amount of weight or to maintain weight loss in spite of ardent persuasion. Therefore, it was evident that some other type of therapy was necessary. We had used "Benzedrine" in several hundred patients during the previous eight years and had found it to be quite effective

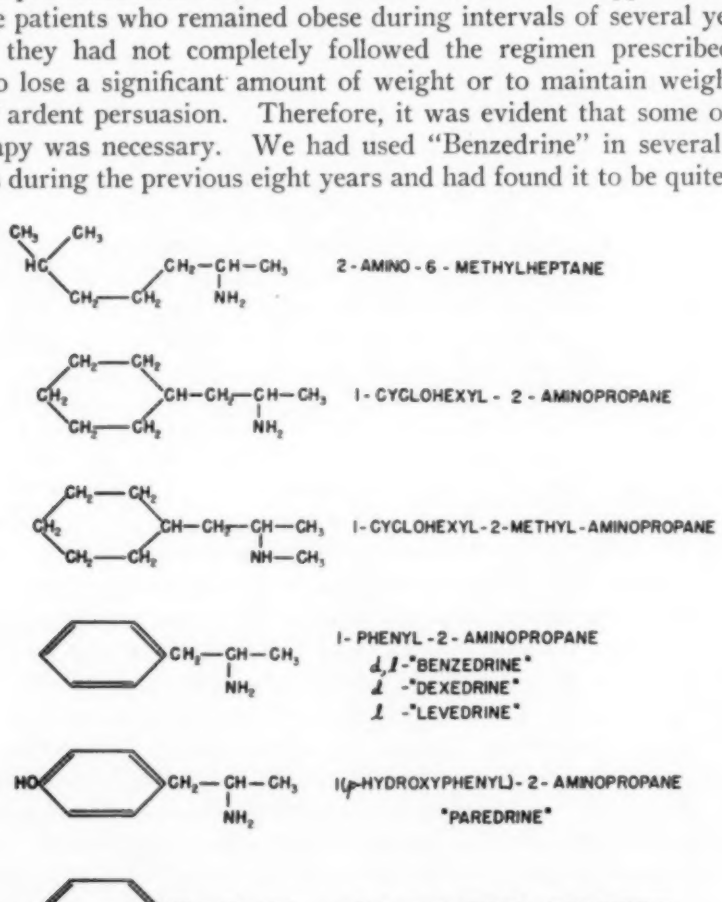
2 - AMINO - 6 - METHYLHEPTANE
1 - CYCLOHEXYL - 2 - AMINOPROPANE
1 - CYCLOHEXYL - 2 - METHYL - AMINOPROPANE
1 - PHENYL - 2 - AMINOPROPANE
d,l -"BENZEDRINE"
d -"DEXEDRINE"
l -"LEVEDRINE"
1(p-HYDROXYPHENYL) - 2 - AMINOPROPANE
"PAREDRINE"
1 - PHENYL - 2 - METHYL - AMINOPROPANE
"DESOXYN"

FIG. 4. Note that all of the compounds can be considered as having an aminopropane radical. Slight variations in structure greatly altered the effect of the compounds.

in promoting weight loss. However, it could not be used satisfactorily in some patients because of its side-effects. Moreover, certain others who took it very enthusiastically at first did not desire to take any more after an interval of several weeks, complaining of such symptoms as nervousness, "crankiness," dizziness, insomnia, depression, and prostration. Consequently, we began investigating other 2-aminopropanes with the hope of discovering ones with the good effects of "Benzedrine" and fewer undesirable reactions.

Compounds Studied and Patients Treated. The compounds used in this study are enumerated in figure 4,* along with the structural formula of each. The structure is basically very similar, the 2-aminopropane radical presumably being an essential portion of the molecule.

A total of 132 patients, of whom 117 were females, was treated. The ages ranged from 13 to 63. Essentially all of the patients were from 50 to 200 pounds overweight. None of them had frank glandular disease, other than diabetes mellitus. Hypertension, heart failure, cerebrovascular accidents, diabetes mellitus, nephritis, epilepsy, and peptic ulcer were complications that existed. Only 18 per cent had not had some form of anti-obesity therapy previously. The other 82 per cent had been treated periodically for several years with diet, thyroid and "Benzedrine." Thirty-five per cent had been treated with "Benzedrine" and 31 per cent with desiccated thyroid. Most of these patients had concluded that they would always remain obese. A good many subjects had become so incapacitated that they had stopped working.

TABLE III

Courses of Therapy with Each Compound

Compound	No. of Courses
1-cyclohexyl-2-aminopropane	96
d, 1-phenyl-2-aminopropane	73
l, 1-phenyl-2-aminopropane	10
d, *l*, 1-phenyl-2-aminopropane	10
2-amino-6-methylheptane	25
1-cyclohexyl-2-methyl-aminopropane	32
1-phenyl-2-methyl-aminopropane	36
1(*p*-hydroxyphenyl)-2-aminopropane	25
	Total 307

Plan of Therapy. A total of 307 courses of therapy was given with the 2-aminopropanes described below, each course varying from two weeks to one year. Fifteen patients were given from six to ten courses with from four to seven compounds. 1-Cyclohexyl-2-aminopropane and d, 1-phenyl-2-aminopropane ("Dexedrine") were used more than were the others (table 3). All therapy was given by mouth in the form of tablets or capsules in the

* We are grateful to the Abbott Laboratories, North Chicago, Illinois for supplying us with "Desoxyn" and to the Smith, Kline and French Laboratories, Philadelphia, Pennsylvania for the other compounds studied.

dosage ranges shown in table 4. Usually two doses per day were prescribed. One dose was given at 10 or 11 a.m. and one at 3 or 4 p.m. The morning dose tended to be larger than the afternoon one. Since most of the patients ate very little breakfast, it did not seem worthwhile to give treatment before this meal. Moreover, with the above dosage schedule an anorexigenic effect was present throughout the 24 hours. In a few individuals it was difficult to inhibit bed-time eating without producing insomnia. Although the greatest weight reduction can be obtained by prescribing a low calorie diet as well as anorexigenic compounds, in this study such a diet was prescribed for only a few patients, since we were interested chiefly in comparing the anorexigenic effect of the several compounds. Therefore, the amount of weight lost, together with the patient's statements of the subjective reactions, served to indicate the relative effects of the compounds. None of the subjects was told what medicine he was receiving. It was possible to evaluate the relative value of the compounds fairly well since several of the compounds appeared identical, some were changed alternately from capsule to tablet form without the patient's knowledge of their identity, the compounds varied in potency, the responses were somewhat proportional to the dosage, and since there was a good deal of rotation in the drugs given to individual patients.

TABLE IV

Dosages of Compounds

Compound	Total Daily Doses (mg.)				Order of Choice
	Range Tested	Large Doses		Optimal Maximal Dose	
		Range	No. of Patients		
d, 1-phenyl-2-aminopropane	5–50	30–50	19	20	1
1-cyclohexyl-2-aminopropane	50–250	200–250	24	150	2
1-cyclohexyl-2-methyl-aminopropane	50–250	200–250	30	200	3
1-phenyl-2-methyl-aminopropane	5–50	20–30	8	15	4
2-amino-6-methylheptane	50–200	200	5	150	5
d, *l*, 1-phenyl-2-aminopropane	10–30	20–30	5	20	6
1(*p*-hydroxyphenyl)-2-aminopropane	20–100	60–100	13	60	7
l, 1-phenyl-2-aminopropane	10–60	50–80	2	60	8

Effects of Treatment. All of the compounds used had good or bad effects or both in most of the individuals. These varied markedly with different drugs, with the same drug given to different individuals and sometimes with the same drug given in the same dosage to the same individual. Only slight changes in the structure of the compounds caused marked change in the biological effects. The desirable effects consisted of anorexia, increased mental and physical activity, a sense of well-being, more ambition and determination and less fatigue. Undesirable reactions observed were nervousness, apprehension, depression, insomnia, exhaustion, headache,

dizziness ("light-headedness"), unpleasant taste, halitosis, burning in throat, heart-burn, dryness of mouth, nausea, vomiting and increased frequency of bowel movements. Other symptoms noted were increased or decreased sweating, increased or decreased thirst, diuresis, general numbness, cold feeling, crawling sensation, rash and tachycardia. A statistical analysis of the frequency of individual symptoms produced by the compounds was unsatisfactory because of variations in dosage and of vagueness in their manifestations. Frequent determinations of the blood pressure were made. In a few cases slight and transient increase in the pressure resulted.

All compounds produced similar manifestations, but the relative intensity of the symptoms varied considerably. Each compound produced in certain patients a pronounced anorexia, weight loss, feeling of well-being, more energy, less fatigue and insomnia. However, in the case of l(p-hydroxyphenyl)-2-aminopropane ("Paredrine") and of l, 1-phenyl-2-aminopropane ("Levedrine") the effect was exerted in only a small proportion of the patients treated and was of short duration. Some of the patients observed that the latter compound produced a very "pleasant effect" even when no weight loss was produced. The "pleasant effect" did not seem to be associated with as much of the irritating, depressing, and apprehensive action as was possessed by some of the other compounds, especially 1-phenyl-2-methyl-aminopropane ("Desoxyn") and d, l, 1-phenyl-2-aminopropane ("Benzedrine"). d, 1-phenyl-2-aminopropane ("Dexedrine") differed from these latter two compounds in its effects upon the central nervous system. It gave the individuals a great deal of pep, ambition, feeling of well-being, and at the same time it caused a marked inhibition of the appetite. The other two compounds, in addition to having these effects, produced apprehension, irritability and lightheadedness which caused the patients to dislike them more. This dislike interfered with the administration of doses large enough to cause marked and continued inhibition of appetite. 1-Cyclohexyl-2-aminopropane exerted cerebral effects somewhat similar to those of the aforementioned two compounds, but it was better tolerated. 1-Cyclohexyl-2-methyl-aminopropane had less of the undesirable cerebral effects than 1-cyclohexyl-2-aminopropane, but, on the average, its anorexigenic effect was not as potent. 2-Amino-6-methylheptane did not cause as many cerebral ill-effects as did "Benzedrine" or "Desoxyn" but its anorexigenic effect was less.

The "unpleasant taste" consisted of a "metallic" or "brassy" quality. Several patients believed that their "breath was bad," and some were so informed by their friends. It was more marked during the interval preceding meals. The alterations in sweating, water intake and output, numbness, cold sensation, dryness of mouth, burning in the throat, and increased bowel movements were all insignificant. Nausea was rare but did occur with each of the compounds except "Levedrine." In a few instances vomiting occurred and necessitated temporary cessation of the drug. When large doses of any of the compounds were given continuously for several months,

certain patients became nervous and exhausted and discontinued the treatment. Then they tended to sleep heavily for several days, at the end of which time they felt in good condition. It was remarkable how much difference in tolerance to the drugs existed. For example, a few patients took 50 mg. of d, 1-phenyl-2-aminopropane ("Dexedrine") daily for several weeks with "no ill-effects." One patient took 50 mg. daily of 1-phenyl-2-methylaminopropane ("Desoxyn") for two weeks with no unpleasant reactions. Similar experiences were obtained with the other compounds. However, most of the patients who received doses equal to the upper range, indicated in table 4, or slightly greater, were bothered by such symptoms as restlessness, anxiety, fullness in the head, headache, dizziness, insomnia, depression and nausea.

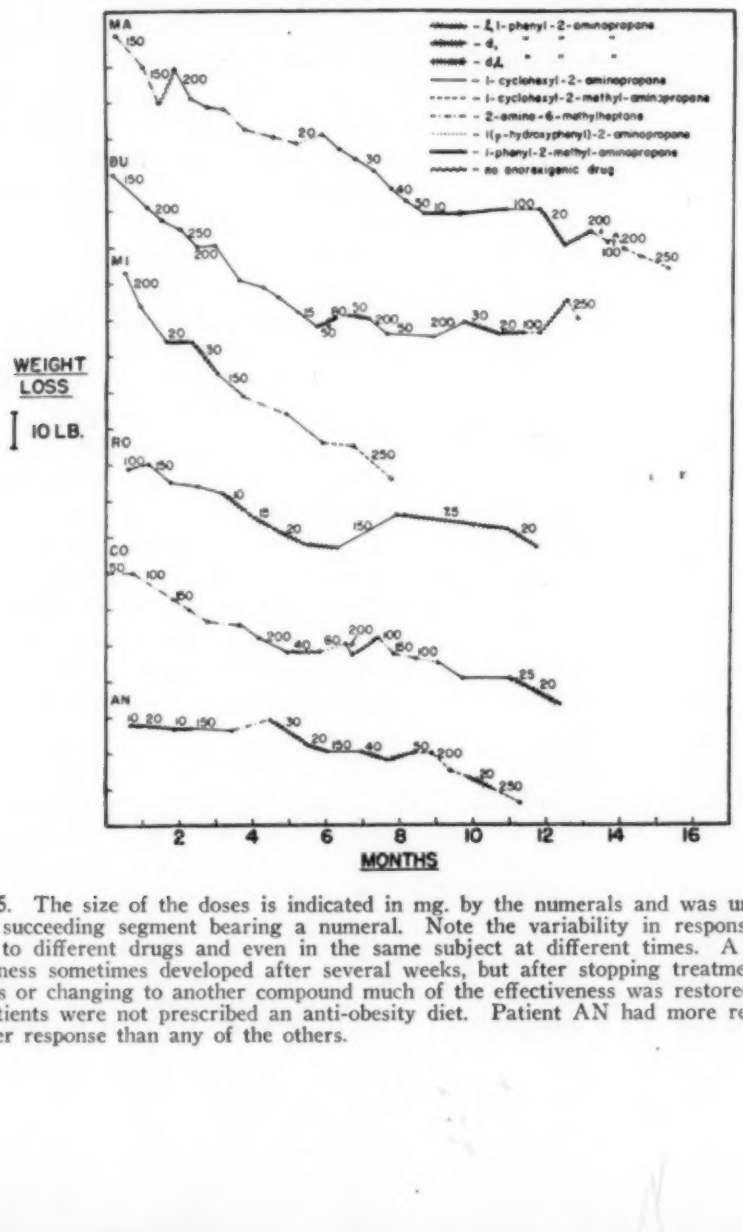

FIG. 5. The size of the doses is indicated in mg. by the numerals and was unchanged until the succeeding segment bearing a numeral. Note the variability in response of individuals to different drugs and even in the same subject at different times. A state of refractoriness sometimes developed after several weeks, but after stopping treatment for a few weeks or changing to another compound much of the effectiveness was restored. Most of the patients were not prescribed an anti-obesity diet. Patient AN had more refractoriness in her response than any of the others.

Late Effects. After taking any of the compounds for several weeks, it was observed that the effects were sometimes much less (figures 5 and 6). By increasing the dosage there was an augmentation of its action, but sometimes a stage was reached when even large doses were without significant effect and if continued they tended to make the patient exhausted. The larger was the initial dose, the sooner did this state of refractoriness develop. Then upon changing therapy to another compound a striking effect was often produced, but after several months a state of refractoriness to the second drug was developed. If therapy with the first drug was resumed, there usually was a much greater effect than at the time of its discontinuance, but not as great as at the time that it was first administered. Sometimes a state of refractoriness to all of the compounds listed in figure 4 developed. After an interval of from 3 to 15 weeks, the initial sensitivity to the compounds was largely regained. No difficulty was encountered in getting the patients to take periods of rest from therapy. Some of their dislike for being without the anorexigenic and stimulating effects of the compounds during these rest periods was relieved by their knowledge that the effects would be increased with the resumption of therapy. No instance of definite habit formation for the drugs was observed. All of the ill-effects of the compounds disappeared within a few days after stopping therapy. There was a distinct variation in the amount of refractoriness developed in different patients. Some patients continued to get the same good effects from the same drug for more than six months. It is desirable to stop therapy with the anorexigenic compounds as soon as the patients lose weight adequately without them; this interval varies from a few weeks to many months.

Selection of Most Effective Anorexigenic Compound. The selection of the best of the aforementioned compounds for the treatment of obesity seems to depend chiefly upon the amount of loss of weight which it produces considered in conjunction with the ill-effects which it provokes. In this situation it does not make much difference about the relative size of the dosage. For example, even though drug "A" may have to be used in quantities 10 times greater than drug "B" to produce the same amount of weight loss, if drug "A" caused fewer ill-effects at the stated dosage it would be preferable, at least pharmacologically.

The patient's conclusion on the subject is highly important, but it must be considered in conjunction with an analysis of its individual effects. A compound which produced only a moderate loss in weight, but permits the patient to be energetic, happy and rested is much better than one which promotes marked weight loss, but also causes restlessness, irritability and insomnia. The patient may take the latter type of compound for several weeks, but at the end of this interval he feels exhausted and somewhat frustrated, so he will decide not to take any more of this type of therapy. On the other hand, although a patient takes a compound which produces certain pleasant sensations and no significant unpleasant ones, if not much weight is lost, he, as well as the physician, will become very much dissatis-

fied with this type of treatment. Moreover, it must be borne in mind that there is a distinct variation in the effectiveness of the compounds in different individuals. For example, a compound which has many good effects and few bad manifestations in one individual may in another individual have few good effects and many bad ones, while in a third subject not much of either effect is obtained. However, considering all of these features, we have indicated in table 4 our order of preference of the compounds. The last two chemicals listed are much less effective than the others, although there is a similarity in structures. d, 1-Phenyl-2-aminopropane ("Dexedrine") is the drug of choice because in most of the patients it produces a moderate anorexigenic effect, yet the unpleasant effects are mild or absent. As far as the others are concerned, it must be remembered that one cannot predict with accuracy in a given patient which one will be most effective and, moreover, it is often wise to shift to other compounds when a state of refractoriness develops. Certain patients became refractory to daily doses as great as 50 mg. of d, 1-phenyl-2-aminopropane ("Dexedrine"), 200 mg. of 1-cyclohexyl-2-aminopropane, 250 mg. of 1-cyclohexyl-2-methyl-aminopropane, 200 mg. of 2-amino-6-methylheptane, 100 mg. of 1(p-hydroxyphenyl)-2-aminopropane ("Paredrine") and 50 mg. of 1, 1-phenyl-2-aminopropane ("Levedrine").

Selection of Dosage. The appropriate dosage of the drugs is one which will bring about a loss of about 1 pound or more per week and yet will not produce enough unpleasantness to interfere with prolonged usage. Only the minimal amount of the compound which is necessary to produce the desired amount of weight loss should be used, since the large doses tend to produce a state of refractoriness sooner than do the small doses and involve an unnecessary expense. In table 4 we have recorded what we consider to be an optimal maximal daily dose of each compound tested. Some individuals took larger doses satisfactorily, while others could not take doses of the size listed. Most of the patients tolerated these doses well for several weeks and experienced a distinct anorexigenic effect. In many instances doses which were only from 50 to 75 per cent of these were satisfactory. The specific dosage had to be regulated in each patient.

Mechanism of Action. The chief mechanism by which the 2-aminopropanes produce a loss of weight is by decreasing the hunger and appetite [12]—an anorexigenic effect. Essentially all of the patients had a decrease in their desire for food throughout the entire day. In this connection it was observed that four patients who were kept in the hospital on a low calorie diet, maintained meticulously constant, lost weight just as rapidly when they were not taking any anorexigenic compound as when taking large doses of them (figure 6 and 7). We found that none of these compounds increased the basal metabolic rate. However, they must increase the total daily consumption of calories as evidenced by the increase in mental and physical activities that are produced. The increase in ambition, determination and feeling of well-being may help the patient to make adjustments in his habit of over-

eating and correct some of the factors which contributed to this habit. In most of the patients, with the usual dosage employed, the decrease in appetite is best not thought of as a toxic effect, since the patient tended to feel better than usual and the ill-effects were generally mild and reversible.

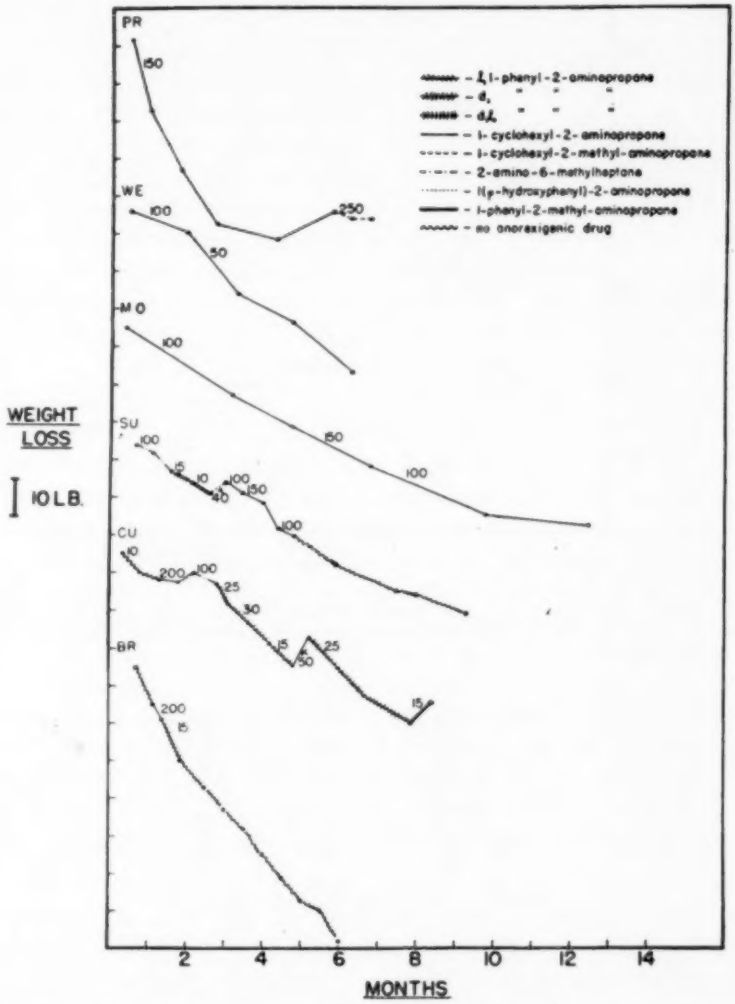

FIG. 6. Note that patients SU and BR lost weight just as rapidly without the anorexigenic compounds as with them. These patients, however, were maintained on low calorie diets. Patient MO took the same compound for a year with equal effectiveness throughout the interval.

There may have been a slight effect on the gastrointestinal tract since some of the patients had an increase in the number of bowel movements, a few experienced nausea and a very few complained of abdominal pain. A few individuals stated that they "went to the table about as hungry as usual,

but found that it took less food to produce a full feeling." There was no significant change in the volume of the stools.

Effects of the compounds upon the volume of urine were inconsistent. During the first few days there tended to be a slight diuresis.

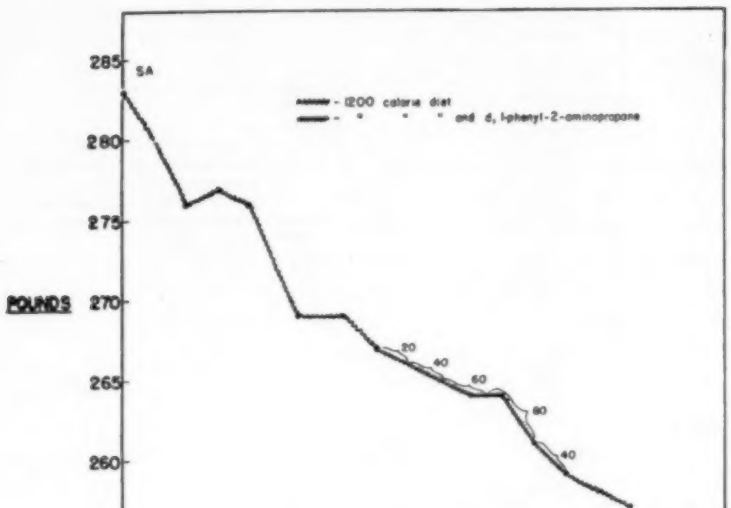

FIG. 7. Note that patient SA lost weight just as rapidly on a carefully controlled 1200 calorie diet as she did with d, 1-phenyl-2-aminopropane given in large doses in conjunction with the same diet.

Several patients volunteered the comment that most of the weight lost while taking the drugs was from their waist and that the amount of reduction of the circumference of their waist was greater than the amount of weight lost would indicate. For example, one subject had a decrease in waist circumference of 6 inches with a loss in weight of only 24 pounds.

SUMMARY AND CONCLUSIONS

Marked obesity interferes seriously with the health and happiness of a vast number of individuals. This fact should be clarified in the minds of obese subjects and their desire to take adequate therapy should be stimulated. Although obesity should be conceived of as a condition of positive energy balance, the factors which contribute to this imbalance, whether emotional, environmental, etc., should be sought and corrected as far as is possible. The patient should learn about relative caloric values of many articles of diet and should have his daily ingestion of food restricted sufficiently to lose the desired amount of weight.

If these objectives are not obtained after the physician has made an ardent effort to pursue the principles just outlined, it is often of advantage

to use compounds of the aminopropane type as adjunctive therapy. These compounds are of aid chiefly through their anorexigenic effect. Consequently, it is quite important that a diet of low caloric value is prescribed and that the patient follow the other features of regimens outlined for obese subjects not receiving drug treatment. The use of the anorexigenic compounds alone does not cause sufficient loss of weight in most subjects.

In this clinic we have used 8 aminopropane compounds in the treatment of 132 markedly obese patients. A total of 307 courses of therapy, from 2 to 52 weeks, was administered. A few patients received as many as 10 courses with 7 different compounds. For this study most of the patients were not placed on a special diet, since it was desired to observe the effects on weight reduction of the drug alone.

Individuals were found to vary a great deal in their response to the different compounds and even the same compound; moreover, a variable degree of refractoriness was found to develop. All of the compounds used had good effects, or bad effects, or both, in most of the patients. The good effects consisted of anorexia, increased mental and physical activity, a sense of well-being, and increased ambition. Undesirable effects were restlessness, apprehension, depression, irritability, insomnia, exhaustion, headache, dizziness, unpleasant taste, halitosis, burning in the throat, dryness of mouth, heartburn, nausea, vomiting and increased frequency of bowel movements. By the appropriate regulation of the dosage most of the patients were made to lose a significant amount of weight without the ill-effects of the compound being very prominent. Considering all of the characteristics of the chemical used, the following three drugs, in order of preference, were chosen as the most desirable ones: d, 1-phenyl-2-aminopropane ("Dexedrine"), 1-cyclohexyl-2-aminopropane, and 1-cyclohexyl-2-methyl-aminopropane. In some patients it is not necessary to use drug therapy for more than a few weeks, because the patient will have become adjusted sufficiently well to continue the regimen without it. When it is necessary to administer the compounds for many months we suggest that after treatment for intervals of about four months there be interspersed periods of from two to four weeks with no anorexigenic drugs. When a state of moderate refractoriness has developed, another one of the compounds should be used. The first compound can later be used effectively.

The good effects of this type of treatment greatly overbalance the ill effects when it is used cautiously in selected cases.

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CASE REPORTS

THE DISADVANTAGES OF SULFONAMIDE COMBINATIONS*

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Recently there have appeared reports in the literature advocating the use of "sulfonamide combinations." [1, 2]

The purpose in giving combinations of these similarly acting drugs has been to reduce the danger of "intrarenal drug precipitation" and "concrement formation." While giving comparatively small doses of each component of a mixture of sulfonamides, the danger of intrarenal drug precipitation should be only as great as if each compound had been administered alone. Yet the sum of the components could be completely effective in eradication of a given infection. This method of sulfonamide therapy at first sight appears very desirable but a case is herewith presented that demonstrates the disadvantages of combined sulfonamide medication.

Case Report

Mr. F. L., a 58 year old building contractor, appeared in my office on February 1, 1947, complaining of burning on urination, frequency and pain at the urethral meatus. These symptoms had appeared 10 days previously and were getting progressively worse. The patient had had extramarital relations about one month before.

His past health had always been "perfect." He had had a hemorrhoidectomy in 1914. Otherwise he had never had to consult a physician.

Physical Examination: The patient appeared ill. He had a tachycardia, pulse 114 and temperature 100° per rectum. His blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. The only pathological finding of any importance was the presence of a heavy urethral discharge. His heart was not enlarged. No mumurs were heard. No costovertebral tenderness was demonstrated. His prostate gland was normal in size.

His urine showed no albumin or sugar. Abundant pus was evident grossly and microscopically. The urethral smear showed a variety of organisms, a few gram negative intracellular diplococci and many extracellular gram negative bacilli and cocci. His blood Wassermann test was negative.

Treatment: The patient was given 100,000 units of penicillin G crystalline at once and this dose was repeated every three hours for three doses. To insure the eradication of his infection he was then advised to take Combisul T.D. (Sulfathiazole-Sulfadiazine Combination, Schering) 1 gram four times a day for five days.

The patient took one gram of the drug before supper and one gram on retiring. That night he also took eight ounces of citrate of magnesia of his own volition. In the morning the third dose of Combisul T.D. was taken with fruit juice. Shortly thereafter the patient began to retch and vomit. He did this continuously for two hours and he suffered a severe chill. His temperature rose to 105.2°. On examination no new physical signs were found. It was decided that the patient had had a sulfonamide fever reaction precipitated by the magnesium citrate purge and the

* Received for publication July 31, 1947.

dehydration resultant from vomiting. Combisul was therefore stopped and the decision was made to continue treatment with penicillin. A blood count, taken at this point, revealed 31,250 white blood cells per cubic mm. with 92 per cent polymorphonuclear cells, 5 per cent lymphocytes and 3 per cent monocytes.

Penicillin 50,000 units was thereupon given intramuscularly every three hours. The urine became much clearer. The purulent discharge disappeared and the temperature went down to 99.8° within 48 hours. Penicillin orally 400,000 units daily was then substituted for the parenteral route and the drug was continued in this manner for one week. The patient meanwhile developed a new complaint. He had a great deal of pain in moving his bowels! He also continued to run a low grade fever. His temperature was 100.6° per rectum. On examination he was now found to have a large, tender, fluctuant prostate gland. A diagnosis of prostatic abscess was made and the patient was advised to have surgical drainage. Penicillin was again resumed parenterally.

On February 14, 1947, Dr. B. Rothhouse * performed a perineal incision and drainage of the prostate. Much pus was obtained perineally and also by way of the urethra. A culture was made of this pus and a Foley retention catheter was inserted into the bladder.

Post-operatively the patient's temperature rose to 104.8° although penicillin had been continued without interruption. It was obvious that this infection was penicillin resistant. On February 16 culture of the pus from the incision and drainage revealed *Escherichiae coli* and *Enterococci faecalis*. Blood culture was negative. A test for streptomycin sensitivity was requested but unfortunately could not be done. However, the organisms in the pus were considered by the bacteriologist to be of a type that is streptomycin sensitive. Streptomycin was thus started, 0.25 gram every four hours. A favorable response was evident the first couple of days but later the temperature went up again and it stayed up between 103° and 104.6° until February 27 at which time after some 24 hours of sulfathiazole (1 gram q. i. d.) inadvertently given, the temperature dropped to 97.8°. Shortly after this the patient had a chill and his temperature rebounded to 104° with the appearance of a macular rash. This reaction was not unexpected since the patient had previously reacted to the Combisul T.D. Sulfathiazole was immediately stopped and streptomycin was now resumed in larger dosage, 0.33 gram every four hours. Later it was again increased to 0.4 gram every four hours. On these massive doses of streptomycin the patient's temperature began to come down by lysis. For the next 15 days the patient's highest temperature was only 100.6° but he had right costo-vertebral tenderness and a consistent pyuria. He also complained of being dizzy all the time (due to streptomycin toxicity). On March 17, 1947, after the patient had shown a temperature of 100° or less for four days streptomycin was stopped. The patient then promptly developed a left epididymitis and his temperature again rose to 103°. Treatment for the next week was expectant in the hope that the epididymitis and the fever would subside spontaneously. Unfortunately, however, the temperature continued to be high and on March 25 streptomycin was resumed. After 24 hours the patient still had a fever of 104°. It was then decided to try sulfadiazine alone. In view of the fact that the patient had had so much of the antibiotics and his condition was still unimproved, and since sulfadiazine had not been tried alone but only in combination with sulfathiazole to which the patient was clearly sensitive, it was considered worthwhile administering sulfadiazine cautiously with equal doses of sodium bicarbonate. The result with the sulfadiazine was remarkable. There was a critical defervescence of the fever. The epididymitis subsided, the pyuria completely cleared in 48 hours and the costo-vertebral tenderness disappeared. No signs of intolerance to sulfadiazine developed. The patient was completely cured and left the hospital on April 3, 1947. On April 22, 1947, when a follow-up examination was made, the patient showed no residual

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evidences of genito-urinary infection but he did display an unsteady gait, a diminution in hearing and he still complained of vertigo due to the streptomycin therapy. His blood Wassermann test was again found negative.

Comment

The above case illustrates the disadvantages in administering a sulfonamide combination. It is reasonable to assume that while the urinary tract disturbances resulting from sulfonamides are relatively dependent upon dosage and can probably be diminished by mixtures of two or more sulfonamides with the dose of each cut in proportion, the sensitivities such as the drug rashes, the drug fevers, the hemolytic anemias and the neutropenias are not related to dosage and should be more prone to occur with such combinations. It has been demonstrated by numerous investigators that the incidence of toxic reactions in general is lower with sulfadiazine than with the other absorbable sulfonamides.[3, 4, 5, 6] Therefore, giving a mixture of sulfathiazole with sulfadiazine should expose the patient to a greater risk of developing a sensitization reaction than sulfadiazine administered alone.

Secondly, with sulfonamide combinations when a toxic reaction does occur, the physician is unable to determine which component drug has been at fault and he may unnecessarily abandon this very useful type of medication whereas, if he were to use the single sulfonamide, in the presence of a reaction he could always cautiously try another sulfonamide.

Since alkalinization of the urine also is very effective in reducing intrarenal sulfonamide precipitation, the necessity of using the sulfonamide combinations would appear to be limited to only such cases as could not take adequate amounts of alkali.[7, 8, 9]

Statistical studies of the comparative frequency of toxic reactions to sulfonamide combinations and sulfadiazine by observers in a position to treat many cases would be desirable.

Summary and Conclusions

A case is herewith presented where a sulfonamide combination was given with a resultant severe thermal reaction. The infection was penicillin and streptomycin resistant and sulfathiazole administered alone caused a toxic reaction but sulfadiazine was completely and quickly effective in eradicating the disease. It is suggested on theoretical grounds that the administration of sulfonamide combinations will enhance the possibility of sulfonamide reactions such as drug rashes, drug fevers, hemolytic anemias and neutropenias. It would appear to be better judgment to give a single sulfonamide with adequate alkali to prevent intrarenal drug precipitation than to give sulfonamide combinations.

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SUBARACHNOID HEMORRHAGE SECONDARY TO A TUMOR OF THE HYPOPHYSIS WITH ACROMEGALY *

By Jack D. Kirshbaum, M.D., F.A.C.P., *Bakersfield, California,* and Bernard M. Chapman, M.D., *Chicago, Illinois*

Cases of acromegaly are infrequently encountered and when seen are looked upon as curiosities. The clinical syndrome of acromegaly was first described in 1886 by Pierre Marie, and the following year Minkowski [1] suggested that the disease was caused by derangement of the hypophysis cerebri. It is well known that acromegaly is associated with eosinophilic adenomas of the anterior lobe of the hypophysis. However, many cases of eosinophilic adenoma of the hypophysis do not manifest acromegalic features nor other endocrine disturbances clinically.

Although most writers [2] state that acromegaly occurs usually between the ages of 20 and 30 years, the author's cases have all been older, the youngest being 35 years and the oldest 74 years. The disease has not been observed to be hereditary; however, Levy [3] noted in a series of cases that 30 per cent showed a familial tendency. The clinical picture usually is influenced by the size of the tumor and its intimate relationship to surrounding structures.

The following case is being reported because of its unusual complication, a subarachnoid hemorrhage.

Case Report

Clinical History. A 35 year old white male was admitted to the University Hospital on April 6, 1938, in a state of coma.

Relatives stated that since the age of 14 the patient's hands and jaw had been large. In the past eight years there had been a marked increase in the size of the hands and jaw and his voice had become deeper. The patient had been married for 10 years and had no children. His wife stated that for the past three years his sexual power had been absent, although he had never been very aggressive sexually. The family history was negative for endocrine disturbances.

* Received for publication November 16, 1945.
This work was done prior to entry on active duty.

He seemed perfectly well until two weeks prior to admission, at which time he began to complain of severe headaches. Heavy doses of aspirin had no effect. This was associated with a severe emotional upset caused by his mother's death. Headaches became more severe, and two days prior to entrance the patient began to have projectile vomiting. The next day relatives stated that he seemed to be sleeping most of the time, could be aroused only with difficulty, and seemed disoriented. He vomited five to six times that day. The next day he seemed worse and was brought to the hospital.

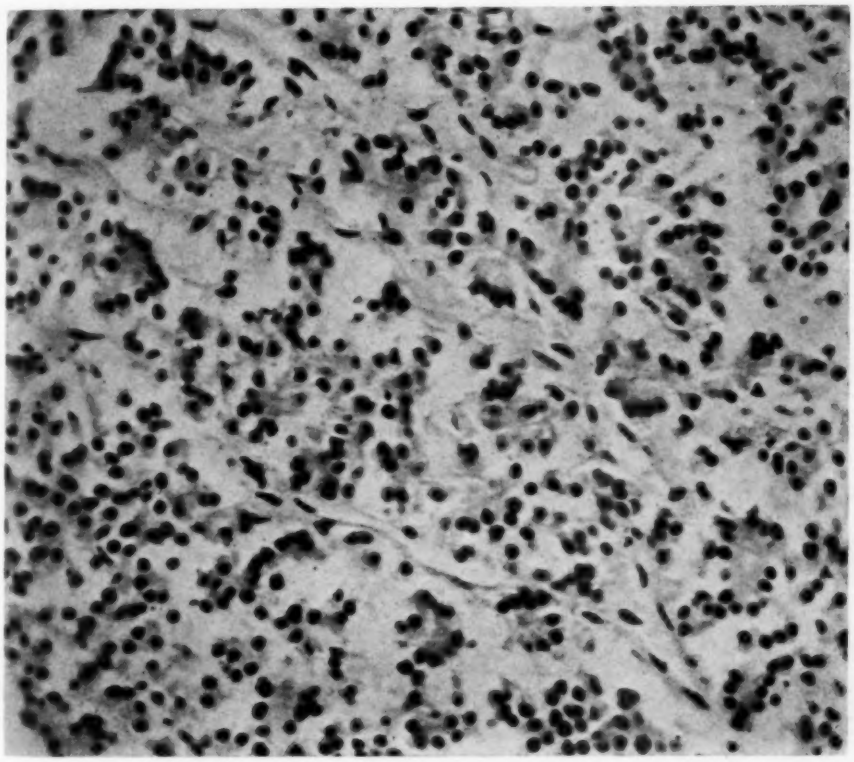

FIG. 1. Section of the tumor composed of acini with fairly regular nuclei.

Physical examination revealed a well nourished, well developed white male in a semicomatose state. The facial features were typically acromegalic. The temperature was 104° F., the pulse rate was 60, and the respirations were very rapid. The head was large and the scalp was covered with hair. The nose was unusually prominent, and the pupils were equal and reacted to light. The lower jaw was large.

The neck was very rigid and the head was extended backwards. The heart tones were distant. The right lower lobe revealed bronchial breathing. The abdomen was negative. The hands and feet were very large. The fingers were sausage shaped. The back was held very rigidly. Both Kernig's and Brudzinski reflexes were strongly positive.

Laboratory. Urine examination was negative. The blood showed a hemoglobin of 80 per cent, red blood cells 4,170,000, and white blood cells 9,500. The Wassermann test reaction was negative. The spinal puncture revealed blood-tinged fluid under pressure. The colloidal gold test was negative.

Roentgen examination of the skull revealed an enlarged sella turcica and eroded clinoid processes. The frontal sinuses were very large and protuberant.

Course. The patient never regained consciousness. He became cyanotic and died nine hours after admission.

Necropsy Findings (Restricted to examination of the skull only). The body was that of a muscular white male. The left side of the mouth showed a slight drooping. The mucosa of the lips and finger nails were cyanotic. The pupils were round and the right was slightly larger than the left. The teeth were in good condition. The head appeared much larger than normal, and the cheek bones and jaw were very prominent. The nose also was large. The skin of the face was deeply pigmented and cyanotic.

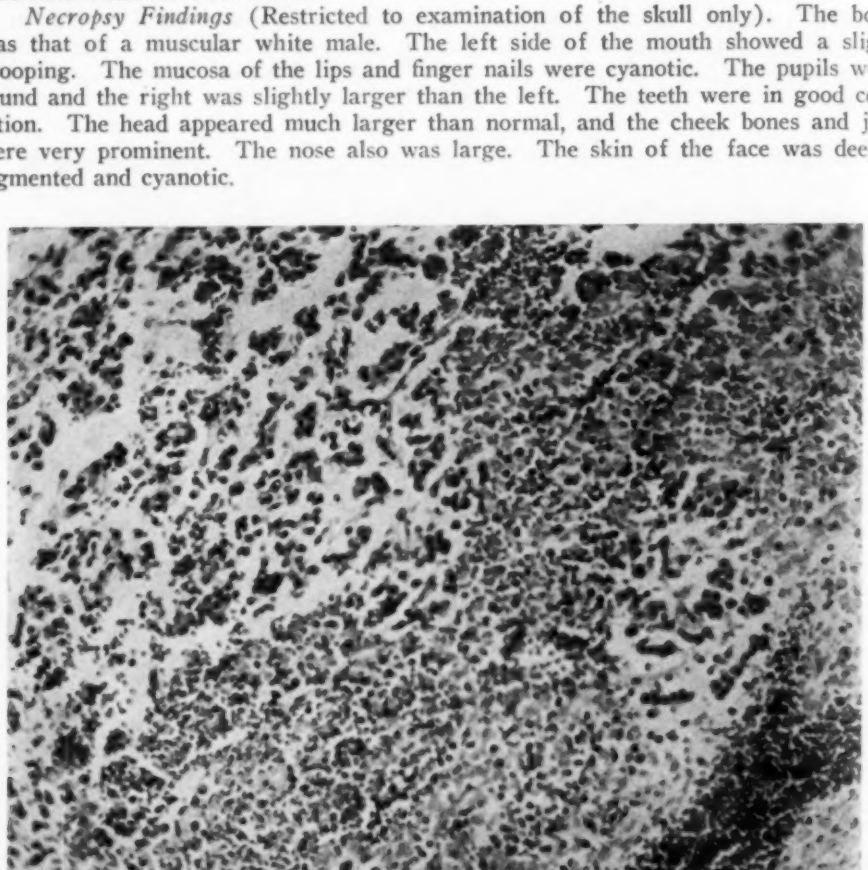

FIG. 2. Section from the surface of the tumor showing areas of necrosis and hemorrhage.

Extremities. The arms extended down to the middle third of the thigh. The fingers were short, very broad (up to 3 cm. in diameter), and the ends were rounded. The middle fingers was 8 cm. long. The legs were short but very muscular.

Brain. The brain weighed 2,640 grams. The consistency was soft, and the convolutions were prominent. Between the meninges there was a recent bloody exudate.

Hypophysis. The hypophysis was transformed into a nodular tumor mass measuring 50 by 35 by 25 mm. It was soft and the surface was discolored purple red. On the anterior aspect there was a cavity 25 mm. in diameter filled with blood. The stalk measured 15 mm. in length and 7 mm. in diameter. The blood vessels at the base of the brain were thin-walled and patent.

The sella turcica was markedly enlarged, eroded, and measured 28 mm. in anterior-posterior diameter, 35 mm. in transverse diameter, and 20 mm. in depth.

Microscopic Description. The tumor of the hypophysis occupied the anterior lobe and was composed of small polygonal-like cells with an ample eosinophilic staining cytoplasm. The nuclei were small, oval to round, and only rarely irregular in size. The cells formed acini which often anastomosed with one another. The stroma of the tumor was loose and frequently contained dilated and congested blood spaces. In some places the tumor cells contained irregular and hyperchromatic nuclei. Other parts of the tumor showed marked regressive changes and contained large areas of extravasated red blood cells and focal areas of necrosis. The tumor was surrounded by a thickened fibrillar capsule which contained numerous dilated blood spaces packed with red blood cells. There were no evidences of malignancy.

Anatomical Diagnoses: (1) Eosinophilic adenoma of the anterior lobe of the hypophysis. (2) Subarachnoid hemorrhage due to necrosis of the tumor. (3) Marked enlargement of the sella turcica. (4) Acromegaly (clinically).

Comment

Subarachnoid hemorrhage as a complication of an eosinophilic adenoma is most unusual. In reviewing the literature a case similar to ours, in which the tumor produced a subarachnoid hemorrhage, has not been found. Bailey [4] does refer to the possibility of the pituitary tumor in acromegaly in its terminal stages of undergoing such changes as degeneration or hemorrhage. Our case is of particular interest in that the tumor leaked blood into the subarachnoid space and clinically suggested the diagnosis of meningitis which was subsequently changed to subarachnoid hemorrhage following spinal puncture.

In a series of eight cases of eosinophilic adenoma of the hypophysis encountered at the Cook County Hospital, Chicago, taken from the files of 12,450 consecutive autopsies, only two manifested the clinical picture of acromegaly. Both cases were males, aged 53 and 74 years. The cause of death in the first case was postoperative pneumonia following a thyroidectomy for a toxic goiter, and in the second case death was due to diabetic gangrene. In both cases the tumor had broken through the capsule; however, histologically the cells appeared regular and orderly.

Acromegaly is usually a chronic progressive disease developing after the age of 20. Its presence may be noted for many years. In spite of the large size of these tumors, sufficient normal tissue is frequently present to carry on most of the normal functions of the pituitary gland.

Eosinophilic adenomas of the pituitary gland are usually soft, nodular, and may show degenerative changes with foci of necrosis and hemorrhage. The tumor may vary in size from a few millimeters to six centimeters in diameter. As the tumor grows larger it may become invasive and thus act as a malignant neoplasm, although histologically the cells lining the acini are orderly with regular oval nuclei and an eosinophilic staining cytoplasm.

Tumors of the anterior lobe of the hypophysis in which the eosinophilic cells predominate manifest clinical symptoms by mechanical pressure of the enlarged tumor on surrounding structures or by perverted activity of the altered anatomical-physiology of the gland. Therefore, such symptoms as blindness, diabetes, impotence, obesity, amenorrhea, sterility, or cryptorchism may occur. The bone changes are usually restricted to the skull and extremities. There is an overgrowth of the bones causing the typical prognathism of the jaw, and an

increase of the size of the hands. Roentgen examination may show proliferative changes of the tips of the fingers described as "tufting." The widening of the sella turcica seen on roentgenogram is fairly common.

Increased metabolic rate is frequently noted in acromegaly and its presence should not be confused with a toxic goiter. The visual disturbances are due to pressure of the tumor upon the optic chiasm, and bitemporal hemianopsia may be noted.

SUMMARY

A case of an eosinophilic adenoma of the hypophysis causing a subarachnoid hemorrhage is described.

The patient was a 35 year old male with clinical features of acromegaly.

The tumor had widened and eroded the sella turcica, and had undergone degenerative changes such as necrosis and hemorrhage. Histologically the tumor was benign.

The clinical picture of intracranial pressure was manifested by headaches, vomiting, rigidity of the neck, stupor and coma.

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KLEBSIELLA MENINGITIS: A CASE CURED WITH STREPTOMYCIN *

By EUGENE M. SCHLOSS, Major, M.C., JAY H. DAVIDSON, Captain, M.C., and KATHLYN C. HILTON, 2nd Lt., W.A.C. (SnC), *Phoenixville, Penna.*

ALTHOUGH Friedländer's bacillus (*Klebsiella pneumoniae*) has been known to attack any system of the body,[1, 2] either as the sole agent of disease or as an etiological *particeps criminis,* it has been found to produce meningitis with comparative infrequency. Ransmeier and Major [3] reviewed the literature in 1942 and found but 29 reported cases, to which they added one of their own; Mori [4] reported a single case in 1943; King,[5] bringing the review up to date in February, 1946, commented on the reports of two additional cases not formally presented and described the process in a case which he had encountered. Thus, there would appear to be a total of 32 reported cases, plus two to which reference has been made on the basis of personal communications,[6, 7] in all of which the high mortality prior to the recent use of antibiotic medication has been a striking feature.

The situation was well summarized by Ransmeier and Major, who wrote that "a few patients with meningitis due to Friedländer's bacillus have recovered after administration of sulfapyridine or sulfadiazine, while formerly the condition was almost certainly fatal." Of the instances in which sulfonamides have been em-

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From the Medical Service of the Valley Forge General Hospital, Phoenixville, Pennsylvania.

ployed, there have been two cures attributed to sulfapyridine [8, 9] and one death,[10] one death in a case treated with sulfanilamide,[3] two cures and one death in cases treated with sulfadiazine,[5, 6, 7] and one recovery reported after the use of "Soluseptazine." [4]

Of present-day antibiotic agents in wide usage, there would appear to be justification for the clinical use of either the sulfonamides, particularly sulfadiazine, or the more recently developed streptomycin. Penicillin has been found wholly ineffective against *Klebsiella pneumoniae* in vitro [11] and hence no encouragement is offered for its employment in vivo. On the other hand, both sulfadiazine [12] and streptomycin [13] have demonstrated a high degree of inhibition against Friedländer's bacillus in vitro and a considerable therapeutic value on clinical application. The striking progress made possible by the recent use of sulfonamides in Klebsiella meningitis has already been commented upon. Herrell and Nichols [14] have reported very favorably on the use of streptomycin in chronic pulmonary suppurative disease and somewhat so on its application in *Klebsiella ozena,* aside from its known value in Friedländer's bacillus pneumonitis, for which its use has recently received official authorization.[15]

It was in this status of knowledge concerning the disease and its therapy that a patient with Klebsiella meningitis was recently hospitalized at the Valley Forge General Hospital.

Case Report

A white male, 21 years of age, had been wounded in Germany on April 14, 1945, by a shell fragment which had entered the left upper face and had emerged through the palatal bone, causing extensive damage to the left cheek, orbit, maxillary antrum, nasal septum and ethmoid cells. This resulted in a naso-orbital fistula for which surgical closure was completed and plastic repair begun. On February 1, 1946 he abruptly developed a generalized convulsion, followed by stupor; he became febrile and exhibited slight nuchal rigidity and an equivocal Kernig's sign. Spinal tap disclosed cloudy fluid under increased pressure, and smears showed a gram-positive diplococcus which, on culture, proved to be pneumococcus, type VI; the same organism was obtained on blood culture. He was treated with penicillin intramuscularly and intrathecally, and sulfadiazine intravenously, and, after a very stormy two weeks, went on to ultimate recovery in all respects in six weeks. It was decided to send the patient on a 90-day convalescent furlough at the conclusion of which further plastic repair of the left orbital deformity would be undertaken.

However, about May 14, 1946, while on furlough, the patient developed an upper respiratory infection, manifested by rhinorrhea, which went on to a purulent nasal discharge with intermittent nasal obstruction. On May 27, 1946 he began to have headache, malaise and fever, and the following day was returned to this hospital in a state of some mental confusion. On admission he was found to be febrile and lethargic, had a temperature of 100° F. orally and a pulse rate of 94 per minute, and exhibited slight nuchal rigidity; the leukocyte count was 27,000, with a differential count of 91 polymorphonuclears and 9 lymphocytes. In view of the past history, the medical officer of the day felt that, in all probability, this represented a recurrence of the pneumococcic meningitis and immediately started treatment with penicillin, 30,000 units every three hours, plus sulfadiazine, 5 gm. intravenously. When lumbar puncture was performed the following morning, the spinal fluid was found to be grossly cloudy but, because of the patient's hyperexcitability, no pressure reading could be made; after drainage of 10 c.c. of fluid, 20,000 units of penicillin were instilled intrathecally. This specimen of fluid showed a count of 9,000 leukocytes,

of which 85 per cent were polymorphonuclears; sugar was 53 mg. per cent, Pandy test 4 plus, and total protein was 415 mg. per cent; smears revealed many pus cells but no organisms; culture, reported later, disclosed *Klebsiella pneumoniae*. The patient continued to run a severe toxic course with temperature elevations spiking to 104° F., and, later the same day, penicillin was increased to 200,000 units every three hours; this change was predicated on our experience with an earlier case of pneumococcic meningitis with a resistant focus (to be reported later). During the next 24 hours the patient became comatose; temperature ranged from 102° to 105° F. (rectal); pulse rate varied from 105 to 130 per minute, respirations from 30 to 48 per minute, shallow and irregular. The absence of any clinical response to medication became obvious. Lumbar puncture was repeated and the spinal fluid pressure was read at 290 mm.; 10 c.c. of cloudy fluid were withdrawn and, again, 20,000 units of penicillin instilled. Culture of this fluid also showed *Klebsiella pneumoniae*, even after the massive dosage of penicillin administered intramuscularly and the instillation of 20,000 units intrathecally, and the continued use of sulfadiazine intravenously. Blood sulfadiazine level after the first infusion was 7.6 mg. per cent, but no subsequent determinations were made because of the condition of the patient's veins.

About four hours after the second spinal tap, the laboratory reported that *Klebsiella* had been isolated in pure culture from fluid drawn at the first tap. The patient then appeared to be in extremis, and it was decided to discontinue both penicillin and sulfadiazine, and to institute streptomycin therapy immediately. Accordingly, the patient was given one million units (1.0 gm.) intramuscularly and the spinal puncture was repeated; 100,000 units of streptomycin dissolved in 10 c.c. of spinal fluid were instilled intrathecally. Thereafter, 500,000 units of streptomycin were injected intramuscularly every three hours, and 50,000 units were given intrathecally every 12 hours. During the next 48 hours, the patient remained critically ill and the temperature fluctuated between 101° and 106° F. (rectal). Spinal fluid remained grossly cloudy and pressure continued above normal levels. Smears made from the first spinal fluid obtained after the original intrathecal injection of streptomycin (12 hours) disclosed encapsulated gram-negative bacilli in profusion, but cultures were negative then and thereafter; the inference was drawn that the organisms seen on smear were already killed but not disintegrated, certainly no longer viable or capable of reproduction. Smears during the next 24 hours showed decreasing numbers of such organisms, and cultures remained sterile. Thereafter, both smears and cultures were negative. Toward the end of the 48-hour period, the patient roused occasionally and took some fluid before again lapsing into coma, and fluid-electrolyte level was maintained intravenously. When, however, it was found that there was no appreciable improvement in temperature or nuchal rigidity, the possibility of continued central nervous system irritation from the intrathecally administered streptomycin was considered, and this avenue of therapy was discontinued. The use of 500,000 units intramuscularly every three hours was maintained over a period of 14 days. Within 12 to 18 hours after discontinuance of streptomycin intrathecally, the clinical status of the patient improved to a point where he was rational and asked for food and water; the temperature dropped to 100.2° F. (rectal); while headache disappeared, the patient continued to complain of "pains all over the body," an effect not unusual during the administration of streptomycin. Thereafter, he continued to improve, the temperature reaching 102° F. the following day, 101° F. during the next 24 hours, and seldom rising to 99.6° F. (orally) after the sixth day of the current illness. It was normal after the fourteenth day. Nuchal rigidity and cloudiness of the spinal fluid cleared progressively, and when last observed, more than two weeks after cessation of all therapy, the patient could be considered cured of the Klebsiella meningitis. Spinal fluid on June 28, 1946 was entirely normal from the standpoint of pressure and appearance, cell count, sugar, protein content, smear and culture, and there were no residual clinical signs of the disease.

Discussion

In the case described, both penicillin, in massive doses, and sulfadiazine, in moderate amounts, were used without any appreciable improvement over a period of about 36 hours, at the end of which time spinal fluid culture still showed a heavy growth of *Klebsiella pneumoniae*. Twelve hours after beginning therapy with streptomycin, the spinal fluid was sterile and remained so thereafter. During the first 48 hours of streptomycin administration, the patient underwent some improvement in that he roused from coma from time to time and became capable of taking small amounts of liquids orally; however, true emergence from stupor, drop in temperature, and subsidence of nuchal rigidity did not occur until 12 to 18 hours after discontinuance of the intrathecal mode of administration. It was our impression at the time that the continued fever and rigidity were due to chemical irritation of the central nervous system by the streptomycin, although Anderson and Jewell [16] had administered it in amounts up to 20,000 units intrathecally without meningeal irritation in a case of tuberculous meningitis. It has been demonstrated by Zintel et al.[17] that comparatively little streptomycin appears in the spinal fluid following considerable intramuscular dosage in the absence of cerebrospinal disease, whereas a substantial amount is demonstrable in the presence of diffuse meningeal inflammation; they cite one instance in which the spinal fluid level of streptomycin in a case of *H. influenzae* meningitis reached 25 units per c.c. after administration of one million units in 24 hours. Our rationale, therefore, in the use of large amounts intrathecally is open to question unless one considers that this patient was apparently in extremis at the time that streptomycin was first instituted, and it was felt that only heroic measures could turn the tide of disease.

It is unfortunate that we had no method of estimating the blood or spinal fluid levels of streptomycin at this installation. However, susceptibility studies made on cultures from this case would seem to justify our use both of streptomycin and of the massive doses employed. Sensitivity tests to streptomycin, penicillin and sulfadiazine were run, using modified methods. For the penicillin and streptomycin, serial dilutions of the drugs were made in cold sterile physiological saline, starting with a concentration of 200 units per c.c. and ending with a concentration of 0.39 unit per c.c. To each tube 3.5 c.c. cold sterile brain-heart infusion broth (Difco) were added and 0.5 c.c. saline suspension of 300 million bacteria per c.c. An 18-hour growth of the test organism on an agar slant was suspended in saline and standardized to 300 million bacteria per c.c. on the Coleman Junior Spectrophotometer at 420 millimicrons. Thus the final concentrations of the drugs ranged from 40 units per c.c. in the first tube to 0.078 unit per c.c in the tenth tube. The series was incubated 18 hours at 37° C. and the last tube showing complete inhibition of growth was taken as the end-point.

In the case of sulfadiazine, serial dilutions of the sodium salt were made in 0.01 N NaOH, beginning with a solution containing 500 mg. per 100 c.c. and ending with a solution containing 31.25 mg. per 100 c.c. To each tube 3.5 c.c. of brain-heart infusion broth and 0.5 c.c. of a saline suspension of bacteria standardized to 300 million per c.c. were added. Thus the final concentrations of the drug were 100 mg. per 100 c.c. in the first tube and 6.25 mg. per 100 c.c. in the fifth tube. The series was incubated and read as above.

In all series a control tube containing 1 c.c. of the final dilution of the drug

and 4 c.c. of brain-heart infusion broth was included to check the sterility of the components of the test.

The results showed the *Klebsiella pneumoniae* to be sensitive to 20 units per c.c. of streptomycin but not to 10 units per c.c., and not sensitive to 40 units per c.c. of penicillin or to 100 mg. per 100 c.c. of sulfadiazine. Thus, in view of the almost invariably fatal outcome of Klebsiella meningitis prior to the use of sulfonamides and the resistance of this particular organism to penicillin and sulfadiazine, it would appear that this patient's recovery was effected best by the administration of streptomycin. It is noteworthy also that a concentration of 20 units per c.c. of streptomycin was necessary for inhibition of the organism in vitro; the implication is obvious that high concentrations of the drug would, therefore, be required for clinical effectiveness.

Summary

A case of Klebsiella meningitis is reported in which streptomycin was employed intramuscularly, 500,000 units every three hours for 14 days and intrathecally with an initial dose of 100,000 units and 50,000 units every 12 hours for three additional doses; total, 56,250,000 units or 56.25 gm. The patient made a complete recovery.

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ESSENTIAL THROMBOPHILIA: REPORT OF A CASE*

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IN this communication we wish to present a case which clinically and pathologically conforms to the disease entity known as "Essential Thrombophilia." In 1937, Nygaard and Brown defined this syndrome and reported five cases in which thrombosis occurred in the vessels of the extremities and in the brain, kidney and heart. The thrombosis occurred without any previously known disease of the vessels involved such as is seen in thromboangiitis obliterans and in arteriosclerosis. The pathological changes in the vessels were minimal and of a non-reacting type. Thrombosis was evident without signs of disease in the intima and in the other coats of the vessel. In two cases a slight cellular reaction in the media and adventitia was seen. The occluding thrombus was not organized. There were infarcts found in the lungs, kidney and spleen.

The major pathological process appeared to involve the stability of the suspension of blood platelets rather than specific disease of the vessel walls. An increased coagulability of the blood plasma and an alteration in the distribution of the serum proteins coincided with the periods of thrombus formation. These findings were not considered to be specific for the disease although they were present in four of the five cases reported. The elevation in the platelet count was considered significant. In two cases the marked increase in the globulin-fibrinogen fraction of the serum proteins was believed to be the factor favoring thrombus formation by reducing the suspension stability of the platelets. In reviewing the literature we noted that Nygaard and Brown were the only ones who reported this syndrome. Because of this we feel that it would be of interest to report the following case.

CASE REPORT

C. K., a 30 year old woman, was admitted to the Medical Service of Dr. A. Louria of the Jewish Hospital of Brooklyn on July 27, 1946 complaining of shortness of breath and continuous pain and swelling of her right lower extremity of three weeks' duration. Her symptoms increased in severity. Three days prior to admission, a bluish discoloration of the skin on the dorsum of her right foot was noted. That day, she complained of pain over the left posterior aspect of her chest.

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Since September, 1945 she had noticed dyspnea on moderate exertion and intermittent swelling of her legs. She had been bedridden since June 11, 1946 and was given digitalis and ammonium chloride for relief.

Her past history revealed repeated attacks of chorea from the ages of 11 to 18. At the age of 23 she had three febrile episodes diagnosed as acute rheumatic fever. The patient did not smoke.

Physical examination revealed an acutely ill, obese white woman. She was cyanotic, dyspneic and orthopneic. Her hair was gray, and she appeared to be much older than her stated age. She was alert and coöperative. Her temperature was 103° F., pulse 112, and respirations were 32. Her blood pressure was 128 mm. Hg systolic and 80 mm. diastolic.

Examination of her thorax revealed diminished to absent resonance over the left base posteriorly. Vocal fremitus was decreased and fine crepitant râles were heard both anteriorly and posteriorly. Her heart was not enlarged. Systolic murmurs were noted over both mitral and aortic regions. Her abdomen was pendulous and her right lower extremity was markedly edematous. The skin down to the ankle was warm and hyperemic. Below the ankle, this area was sharply demarcated from a cold, intensely cyanotic foot. The pulsations of the femoral artery were present bilaterally. Pulsations of the popliteal artery and the more peripheral vessels were absent on the right.

Oscillometric readings taken on July 27, 1946 revealed no oscillations at the right knee and ankle. On the left, the readings were 3.5 at the knee and 1.5 at the ankle. On July 28, 1946 large vesicles filled with thin, yellow fluid were noted on the dorsum of the right foot. Splanchnic and paravertebral blocks using 1.5 per cent metycaine were performed at L.1 to L.4. Following injection, there was symptomatic relief and a noticeable lightening of the mottled areas of skin which had developed above the ankle. There was a recession in the intensity of the cyanosis of the foot. On July 31, 1946 her temperature rose to 106° F., and she was irrational. Sensation in her toes was absent. The skin was black and dry up to the metacarpophalangeal joints. She died the following day after her temperature rose to 108° F. Her respirations were noted to be irregular and spasmodic before death. She had received penicillin and papaverine since admission.

Examination of the urine was negative. Blood study on July 28, 1946 revealed a hemoglobin of 55 per cent with 3,340,000 red blood cells and 20,950 white blood cells. Of these, 83 per cent were polymorphonuclear leukocytes, 4 per cent were band forms, 9 per cent were lymphocytes and 4 per cent were monocytes. Eight normoblasts were counted. Poikilocytosis, anisocytosis, polychromatophilia and achromia were evident. The Klein reaction was negative. Blood sugar was 112 mg. per cent, urea nitrogen 33.4 mg. per cent, total protein 6.10 per cent, albumin 3.37 per cent, and globulin 2.73 per cent. The A/G ratio was 1.2.

The blood cultures were sterile.

Skin temperatures taken on July 31, 1946 revealed values of 79°–80° F. over the toes and dorsum of the foot on the right as compared to values of 90°–90.5° F. on the left. The calf temperatures were 91° F. on the right and 93° F. on the left.

During the two days preceding death, the temperature, pulse and respirations rose steadily.

The clinical diagnosis was phlebothrombosis and thrombophlebitis of the right lower extremity; embolus, right popliteal artery; bronchopneumonia, left lower lobe; rheumatic heart disease and obesity. Thromboangiitis obliterans, although rare in females, was also mentioned as a possible diagnosis.

Necropsy. Gross findings: The postmortem examination revealed a massive pitting edema of the entire right lower extremity. The skin of the foot up to the malleoli was purple-red and gray and contained several collapsed bullae. The toes were blue-black, dry and wrinkled.

The heart weighed 380 grams. There was a large amount of subepicardial fat and fatty infiltration of the right ventricular wall was evident. The valves were grossly normal. There was no evidence of rheumatic heart disease and no mural thrombi.

A large, twisted yellow and red-purple embolus was removed from the pulmonary arteries. There were multiple old and fresh infarcts in the left lower lobe of the lungs. Both lower lobes were extremely congested.

FIG. 1. Section taken through the walls of the femoral artery showing the bland thrombus, T, the media, M, and the adventitia, A. The collection of round cells in the central layers of the adventitia is well demonstrated. Hematoxylin and eosin. × 35.

The spleen weighed 480 grams and was extremely friable. It contained large old and recent infarcts. The splenic artery in its entire length was occluded by a firm, yellow, gray and red thrombus. The splenic vein at the hilus was filled with a soft red-purple clot. Along the posterior inferior surface of the pancreas, the vein contained an old organized and well canalized thrombus.

The right femoral artery was occluded by a pink and yellow thrombus that extended peripherally into the popliteal vessels. The right iliac, femoral and popliteal veins were distended with a red-purple, soft, friable thrombus that in part was adherent to the intimal surface. There was no evidence of fibrosis or tissue reaction about the neurovascular bundle.

Microscopic findings: The femoral artery was occluded with a thrombus composed of hyalinized platelets, fibrin and red blood cells. There were early signs of organization at the periphery of the thrombus. The media showed a normal arrangement of its fibers. Immediately peripheral to the fibers of the media was a zone of partially fragmented acidophilic collagenous tissue. In the interstices there were

FIG. 2. High magnification of the zone of adventitia immediately adjacent to the media showing the cellular infiltration. × 600.

scattered small and large reticulated nuclei resembling fibroblasts. Similar cells were seen in smaller numbers about the vasa vasorum (figures 1, 2). A small calcific plaque was seen in the media beneath a slightly thickened intima. The femoral vein showed a similar and less prominent type of infiltration.

In a preparation from the popliteal artery an identical zone of partially fragmented collagenous tissue with interspersed round cells was noted. The intima was moderately thickened. Among the fibers of the media and adventitia of the popliteal

vein, occasional lymphocytes and plasma cells were evident. No unusual reaction was observed about the tibial nerve.

In a preparation from the splenic artery, the thrombus showed no evidence of organization. Signs of intimal reaction were absent. The cellular infiltration of the adventitia was similar to that in the femoral vessel. The splenic vein contained a thrombus of the bland type described above. Scattered among the fibers of the media and adventitia were the chronic inflammatory cells already noted.

Discussion

In this case there was no history of trauma, no evidence of acute infection, and no pathological changes in the heart to account for the widespread thrombosis involving the vessels of the right lower extremity, spleen and pancreas. Microscopic examination revealed the minimal tissue reaction described by Nygaard and Brown as characteristic of essential thrombophilia. Unfortunately, platelet counts and studies of plasma coagulability were not made. The plasma proteins, however, showed the increase in the globulin fraction described by these authors in their report.

Summary

We are presenting a case in which multiple thrombi occurred in vessels of the right lower extremity, the spleen and pancreas in a 30 year old woman. The history and microscopic findings were characteristic of the syndrome called "essential thrombophilia" as described by Nygaard and Brown.

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IDIOPATHIC STEATORRHEA: WITH REPORT OF A CASE OF WHIPPLE'S DISEASE *

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That diarrhea is not infrequently associated with diseases in organs other than the colon has been appreciated for a long time. Thus, diarrhea in hyperthyroidism and occasionally in diabetes [1] and in Addison's disease is well known. Of greater pertinence is the frequency of diarrhea or steatorrhea in such deficiency diseases as sprue, pellagra, and pernicious anemia. In recent years some evidence has been presented pointing towards the identity of sprue, tropical or nontropical, celiac disease, and idiopathic diarrhea. This view is epitomized in Hane's [2, 3] statement that celiac disease is to sprue as cretinism is to myxedema.

Disturbing to this unitarian view has been the lack of uniform pathological findings. Thayssen [4] in discussing the pathological findings in sprue emphasizes the inconstancy of small bowel atrophy in that disease. The very name "sprue-like syndrome" suggests that a variety of pathological lesions is grouped together because of a similar clinical course.

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Although steatorrhea is a sine qua non for the diagnosis of sprue, other diseases than sprue may have steatorrhea. Bargen and his associates [5] have emphasized the lack of pancreatic enzymes as a cause of steatorrhea, and have demonstrated the diagnostic importance of determining the enzyme content of duodenal juice. Fibrocystic disease of the pancreas in children similarly may be distinguished by a diminution of pancreatic enzyme. Of particular interest is the manifestation of steatorrhea in Hodgkin's disease of the mesenteric glands as described by Fairley and Mackie.[6] Tuberculous mesenteric adenitis [7] and jejunoileitis [8] have also been observed to produce a sprue-like syndrome. In an excellent study by Miller and Barker [9] of 33 patients with the sprue syndrome who responded to an antisprue régime, two died after six and 21 months respectively. One of these patients was found to have tuberculous peritonitis, and the other carcinoma of the pancreas.

In recent years, Whipple's disease [10] or lipophagic intestinal granulomatosis has aroused some interest. The classical syndrome as described by Whipple consists of steatorrhea, arthritis, anemia, emaciation, an enlarged abdomen, and skin pigmentation. Pathologically, in addition to panserositis, there are enlarged intestinal villi filled with lipids, and enlarged mesenteric nodes showing dilated sinuses giving both the lymph nodes and the villi a swiss-cheese pattern. To date 17 [10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23] cases fulfilling the above general criteria have been described, though some of these lack such important symptoms as diarrhea, steatorrhea, or arthritis. Although all the cases described showed mesenteric adenopathy, not all presented the classically described dilated villi.

Only one case [21] has so far been reported ante mortem and that was following an exploratory laparotomy. The antemortem diagnoses of Hodgkin's disease, ulcerative colitis, Boeck's sarcoid, and leukemia were not infrequently entertained, and reflect the diagnostic difficulties. While all cases reported have shown a varying degree of anemia, one case had an antemortem diagnosis of lymphatic leukemia, and another a diagnosis of lymphatic leukemia and hemolytic icterus for which a splenectomy was done.

Captain Marcell Patterson, Medical Corps, then on our service, was the first to suggest that our patient might have lipophagic intestinal granulomatosis after comparing the clinical picture with that of a recently reported case.[22]

Case Report

A 37 year old white soldier, stationed in Italy, was well until August 1944 when he began complaining of weakness and frequent bowel movements. These bowel movements occurred mostly during the morning hours; borborygmi and tenesmus were present most of the time. There was no melena; the stools were usually watery, at times soft and occasionally formed. The patient's best weight was 130 pounds; when he returned to the United States in October 1944 it had decreased to 100 pounds. On one occasion his liver was considered to be slightly enlarged. Repeated stool examinations were negative for parasites, ova and occult blood. In March 1945 gastrointestinal roentgenographic studies revealed the stomach and duodenum to be normal except for the presence of hypermotility and an atypical pattern of the small bowel. Roentgen studies following a barium enema were reported as normal. In June 1945 a peritoneoscopy was done, and "yellowish plaques" were described on the liver. These plaques were seen at a subsequent laparotomy at which time a biopsy of the liver and of the mesenteric nodes was taken. Microscopic examination of this biopsy was interpreted as "a subacute inflammatory reaction involving the liver and Glisson's capsule." Unfortunately this tissue was not available for review.

The patient was transferred to Percy Jones General Hospital in October 1945 with a formal diagnosis of cirrhosis of the liver. That the formal diagnosis was only an administrative label was obvious from the other diagnoses entertained, such as schistosomiasis, histoplasmosis, and leishmaniasis. His complaints were essentially as given above. The patient gave no history of arthritis.

TABLE I

Date	R.B.C. (In millions)	W.B.C.	Hb. %	Neutrophiles	Lymphocytes	Eosinophiles	Basophiles	Monocytes	Sedimentation Rate
Oct. 5, 1944	3.82	6150	70	78	16	4	2		57
Oct. 31, 1945	4.16	7750	66	76	20	1		3	37
Nov. 15, 1945	3.01	3700	55	75	25				
Dec. 3, 1945	2.94	6800	58	81	19				15
Dec. 13, 1945	3.2	4200	54	78	18			4	13

Examination. The patient was a markedly emaciated man with a dry, sallow, yellowish skin. There was no icterus. His weight was 80 pounds. The tongue showed slight atrophy. The heart and lungs were essentially negative. There were thrombosed veins in both arms from intravenous administration of blood, glucose and

FIG. 1. Gross appearance of the liver and spleen showing the shaggy exudate over the liver and spleen capsules.

plasma. The blood pressure was 90 mm. Hg systolic and 60 mm. diastolic. There was no abdominal tenderness. The liver, spleen, and kidneys were not palpable. There was no evidence of ascites. There were no enlarged abdominal veins. The

muscles showed marked atrophy. Reflexes were normal. There was minimal edema of both legs.

Laboratory Findings. Blood counts were as shown in table 1. Urine examination showed an occasional trace of albumin, with a specific gravity of 1.019, and no sugar; microscopic examination was negative. The non-protein nitrogen was 29 mg. per cent, cholesterol 66 mg. per cent; cholesterol esters 38 mg. per cent; total proteins 4 grams per cent, albumin 2.7 grams per cent; globulin 1.3 grams per cent; A/G ratio 1.5 : 1; calcium 8.7 mg. per cent; phosphorus 2.8 mg. per cent; alkaline phos-

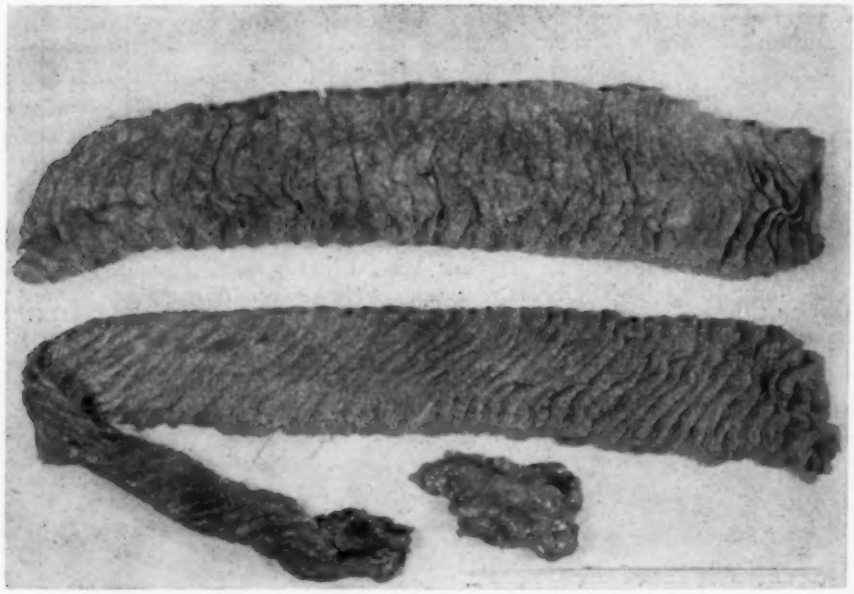

FIG. 2. Gross appearance of the thickened small bowel. At the bottom of the figure note the mass of enlarged mesenteric nodes.

phatase 8.6 Bodansky units; serum amylase was 65 Somogyi units. Stool examinations were negative for ova, parasites and occult blood; 57 per cent of the dried weight was fat, of which 28 per cent was fatty acid (present as stearic acid) and 72 per cent was neutral fat. A sugar tolerance test was as follows: Fasting 76 mg. per cent, after one-half hour 101 mg. per cent, after one hour 109 mg. per cent, two hours 108 mg. per cent, three hours 83 mg. per cent, four hours 76 mg. per cent, and at five hours 93 mg. per cent.

Roentgenographic Examination. Roentgenographic examination of the stomach was negative. Serial films of the small bowel showed marked segmentation, edema of the valvulae conniventes, and marked laking and stasis of barium in the small bowel. Roentgenographic studies following a barium enema revealed nothing abnormal. A chest roentgenogram showed pleural thickening in the right costophrenic sulcus.

Course in Hospital. Because the patient ate better when he was permitted to select his own diet, any attempt to regulate his food had to be abandoned. His diet was supplemented by vitamins and liver extract. He was also given frequent blood transfusions, plasma and glucose intravenously. At first the patient gained some weight, the stools became more formed and less profuse, and the borborygmi and tenesmus were calmed. But whatever veins were available soon became completely thrombosed so that intravenous therapy had to be discontinued. The patient ran a

FIG. 3. Microscopic appearance of the small bowel. Note the enormously enlarged villi. Some vacuoles can be seen in the upper left corner.

low grade fever for which penicillin was given without relief. An area of redness 1 cm. in diameter appeared along the lateral margin in the midportion of the right leg. This area was covered by scales and resembled a psoriatic lesion. A similar lesion appeared on the right upper arm. Biopsy of the latter was interpreted as "slight hyperkeratosis and chronic dermatitis." The lesion on the leg disappeared spontaneously. The patient continued to run a fever of 102° F. to 103° F. The number of bowel movements was rarely more than seven daily; they were a battleship gray

FIG. 4. Microscopic picture of the small bowel showing the vacuoles in the villi. Such vacuoles were also present in the submucosa.

in color and not foamy. About a week prior to his death he began complaining of a chest pain and a severe cough. He finally died in January 1946, 17 months after the onset of his illness.

Postmortem Examination. The postmortem examination was done eight hours after death. Chest: Numerous dense fibrous adhesions obliterated both pleural cavities and very little fluid was present. Both surfaces of the pleura were covered by a grayish white feathery exudate. Numerous areas of consolidation were noted in both lower lobes. The upper lobes appeared normal. The tracheal and bronchial

nodes were slightly enlarged. The heart weighed 375 grams; only about 20 c.c. of fluid were present in the pericardium. A few dense fibrous adhesions attached the pericardium to the anterior portion of the right ventricle. The pericardial surface was dull and was covered with a brown fibrinous exudate. The chordae tendineae were shortened and thickened. Abdomen: There were about 300 c.c. of cloudy thin fluid in the peritoneal cavity. The peritoneal surfaces were dull. There was marked mesenteric lymphadenopathy. Some of the nodular masses were 6 by 3 by 2.5 cm. The nodes were discrete and had a rubbery consistency. The liver weighed 1460

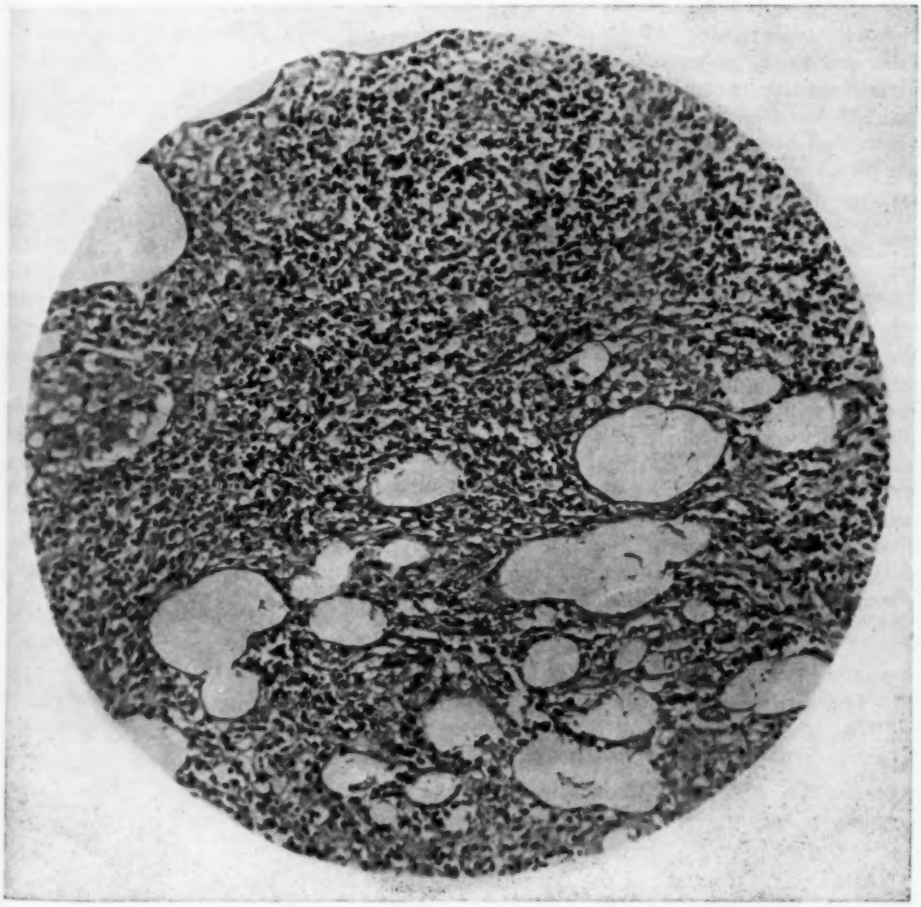

FIG. 5. Microscopic picture of a mesenteric node. The normal architecture has disappeared, the follicles are poorly preserved. Note the marked vacuolation.

grams. The external surface was covered by a shaggy fibrinous exudate very similar to that seen on the pleura and pericardium (figure 1). This exudate measured about 2 mm. in thickness. The normal lobular markings were somewhat obscured. No scarring or tumor was found. The gall-bladder appeared normal, the ducts were patent, and no stones were present. The spleen weighed 210 grams, and was covered with an exudate similar to that seen on the liver; it cut with increased resistance. The stomach was not grossly abnormal. The wall of the small intestine was markedly

thickened and edematous, most marked in the jejunum but also present in the ileum and duodenum. The entire small bowel was about twice the normal diameter (figure 2). The mucosa in particular was thickened and studded with granular grayish white flakes of various sizes which projected above the mucosal surface. The valvulae conniventes were very prominent and a lipoid substance exuded after the mucosa was cut. Gross examination of the colon, kidneys, pancreas, adrenals and brain showed no abnormalities.

The significant microscopic findings were limited to the small intestine, pleura, lungs, liver, lymph nodes and spleen. Small intestine (figures 3 and 4): All layers were thickened; some of the villi were three to four times wider and longer than normal. Large irregular vacuoles of various sizes were scattered throughout the villi, and in the submucosa large mononuclear foam cells were present. Fat stains identified these as cells containing lipids. Brunner's glands appeared normal. Mesenteric nodes (figure 5): The normal architecture was replaced by large irregular vacuolated areas which appeared to be lined by endothelium, and presented a swiss-cheese pattern. Only small islands of normal lymphoid cells remained. Numerous large mononuclear macrophages were noted showing a foamy cytoplasm. An occasional giant cell was noted. The lymphoid sinuses were greatly dilated. Lipoid globules were noted in the endothelial-lined cystic spaces. Liver: The capsule was irregularly thickened and lace-like villi projected from the endothelial surface. The fibrillar projections were lined by endothelium and contained lipoid and foam cells. The liver showed congestion about the central veins and moderate cell infiltration in the portal areas. The liver cells were granular, and fat vacuoles and foam cells were scattered throughout. Spleen: The splenic capsule showed the same appearance as that of the liver. The pulp showed congestion and condensation of the pulp reticulum. The follicles were poorly preserved. Lungs: The lungs showed patchy areas of consolidation in which the alveoli were distended with an exudate of round cells, plasma cells, large mononuclear cells and an occasional polymorphonuclear leukocyte. The exudate over the pleura and pericardium was identical with that described for the liver capsule. The other organs showed no pertinent changes. The pathological diagnoses were: (1) Intestinal lipodystrophy (Whipple's disease); (2) bronchopneumonia.

Discussion

The pathologic physiology of this disease is not known. For clinical and pathologic reasons this disease does not fit into any of the metabolic disorders such as Niemann-Pick, Hand-Schüller or Gaucher's diseases. The microscopic appearance suggests mesenteric obstruction to the lymph flow. The shaggy structures on the serous surfaces which on microscopic examination look like extensions of lymph channels, and the pleural and pericardial adhesions suggest an attempt on the part of the lymphatics to gain a new access to the veins. That the attempt is partially successful is evidenced by the relatively long duration of the disease and by the absence of chyle in either the thorax or abdomen; that the attempt is not quite successful is evidenced by the steatorrhea and markedly dilated lymphatics suggesting increased pressure within them, and of course by the patient's demise.

Where the lymphatic obstruction occurs must vary in each case. That occlusion of the thoracic duct is not necessarily the cause is evident by the findings of a patent thoracic duct where the latter was looked for, and in the absence of signs of lymphatic obstruction in diseases where the thoracic duct was actually occluded. The obstruction may be present at any point between the mesenteric nodes and

the opening of the thoracic duct into the subclavian vein. That this disease is so rare is probably due to the relative ease with which the lymph channels produce new anastomoses with the veins. Thus, Blalock and his associates,[24] in attempting to block the return of the lymph into the veins by 257 operations on 52 dogs and 22 cats, were successful in producing complete obstruction in only two animals. If the thoracic duct is occluded, new openings are made by the lymphatics into the inferior vena cava so that drainage of the former into the latter is satisfactorily accomplished.

A certain degree of similarity between regional enteritis and Whipple's disease suggests itself. In this respect, experiments of Reichert and Mathes [25] are of interest. These workers produced localized obstruction in the mesenteric channels, thus producing in the ileum a gross and microscopic picture not unlike that seen in regional enteritis. They believe that ileitis is produced by localized mesenteric lymph obstruction. It is conceivable that if obstruction in regional ileitis were distal to the mesenteric nodes and so extensive that lymphatic drainage from most of the small bowel were impaired, the microscopic appearance would be no different from that seen in Whipple's disease. The projection on the serous surfaces, the distended channels in the lymph nodes, and the presence of a large amount of lipid material are merely expressions of increased lymphatic obstruction. There is no impairment of fat absorption in regional ileitis because there is enough normal bowel left to accomplish this task satisfactorily.

Conclusions

1. A case of Whipple's disease is reported. In general, it substantiates the clinical pattern of the disease as previously reported.

2. Diagnostic proof can be obtained only by laparotomy, if an exploratory operation is done when a disease other than Whipple's is suspected, or on postmortem examination.

3. It is suggested that the pathologic physiology in Whipple's disease differs only in degree from that of other diseases in which there is lymphatic obstruction of the small intestine.

4. The rarity of Whipple's disease is due to the unusual ease with which lymphatic channels are able to establish new communications with the veins.

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CIRCULATORY COLLAPSE FOLLOWING INTRAVENOUS ADMINISTRATION OF NICOTINIC ACID (NIACIN) *

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Nicotinic acid has come into widespread use not only because of its importance in the vitamin B complex but also because of its side action, vasodilatation. It is generally considered to be of low toxicity either given by mouth or by vein

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and few untoward reactions have been reported. Some patients complain of the flush, itching, and sense of heat following either oral or intravenous administration and when doses sufficiently large to produce these signs of vasodilatation are given the patient should be told beforehand that the above phenomena will appear. These signs are desired and do not constitute toxic effects. Experimentally the difference between the therapeutic and toxic dose is very large.[1] An increase in skin temperature has been produced by reason of the increased blood flow. There are no regular changes produced in the blood pressure, pulse rate, respiration, oxygen consumption or electrocardiogram. I have administered the drug to patients with essential hypertension and followed them through the period of vasodilatation with frequent blood pressure and pulse rate determinations. No significant fall in blood pressure or change in pulse rate was found. A few patients have complained of dizziness following intravenous administration on resumption of the upright position. However, as this was the presenting symptom in most of these patients dizziness was not considered to be due to the drug.

Niacin has been advocated for its vasodilating properties in numerous conditions. Ménière's syndrome and migraine have probably received more attention than other conditions. I have used the drug in numerous patients with these syndromes and the reported patient is the only one manifesting a reaction. Pelner [2] reports two patients in whom anaphylaxis occurred following intravenous administration of niacin. Both of these patients had prior medication with niacin or niacinamide and had unrevealed signs of previous mild allergy to the drug. Both of his patients recovered following prompt administration of epinephrine.

Case Report

This patient was white, a male 65 years old who complained of marked dizziness and vertigo for seven to ten days. He had no tinnitus or headaches. He gave a history of chronic cough which was productive of a large quantity of gray sputum in the morning. He had dyspnea on slight exertion. Three months previously he had been hospitalized for accentuation of cough and dyspnea. Roentgenographic studies gave evidence of a pneumonitis and it was also felt that he had early congestive heart failure. He improved following hospitalization for one month. Later roentgenographic studies showed disappearance of abnormal shadows in the lung fields. However, he continued to have cough and exertional dyspnea. He gave no personal history of allergic manifestations; but one sibling had severe chronic bronchial asthma. Another sibling has severe congestive heart failure. The patient had taken niacin previously in multiple vitamin preparations.

He appeared to be chronically ill and poorly nourished. His complexion was markedly sallow. He had no dyspnea at rest. A prominent arcus senilis was present. There were a few basal râles posteriorly. The apex beat of the heart was in the fifth interspace at the midclavicular line. The rhythm was regular, rate 90 per minute, and no murmurs were present. Blood pressure was 130 mm. Hg systolic and 80 mm. diastolic. The peripheral arteries were tortuous and hard. Examination of the oral cavity, abdomen, and rectum gave findings consistent with the patient's age. I considered that he had a disturbance involving his labyrinth, and that therapy with niacin was indicated.

He was placed in the recumbent position on the table and niacin 10 mg. per c.c. (Lilly) was started intravenously. This was given slowly as is my usual procedure. No flush was noted. When he had received 25 to 30 mg. of the preparation he complained of feeling faint and that he was blacking out. His voice was less strong. He had become definitely cyanotic. His pulse became rapid, weak and then imper-

ceptible. His respirations were slow and shallow and his skin was cold and clammy. He appeared to be in a definitely precarious position. The niacin was discontinued at the onset of these signs and 0.5 c.c. of epinephrine was given intramuscularly. His pulse again became palpable but continued weak and rapid. He was given an additional 0.3 c.c. of epinephrine in 10 minutes. His color, pulse, and respirations slowly improved and at the end of an hour he appeared to be out of danger. He told me after this occurrence that a few days earlier while in a barber shop for a shave he almost blacked out when the barber chair was changed to the recumbent position. He was unable to stay in this position. However, when the reported incident occurred in my office he had been recumbent for several minutes before circulatory failure occurred, so I am inclined to feel that recumbency itself was not causative. At no time did he have pain or any choking feeling in his chest. He was able to walk from the office about two hours after the reaction occurred. He had no recurrence of circulatory failure.

Summary

A patient manifesting severe shock during administration of niacin is reported. Circulatory stability was reëstablished at the end of one hour; epinephrine was promptly injected at the onset of the reaction.

Niacin is a drug of low toxicity and reactivity. The possibility of sensitivity should be considered. If the drug is given intravenously, slow administration is advisable with the patient under continuous observation.

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EDITORIAL

LOWER NEPHRON NEPHROSIS

INTENSIVE study, beginning in 1941,[1] of the clinical aspects, pathology, and abnormal physiology of the crush syndrome led soon to the realization that the renal disturbances were not peculiar to this entity but were, in fact, to be observed in many diseases. Bywaters and Dible [2] drew attention to the fact that the syndrome, which they had previously thought to be a new one, had as a matter of fact been recognized by German clinicians and pathologists in World War I. A review of these cases had been published in 1923 by Minami.[3] Moon [4] observed that many of the predominant features of the syndrome were quite well known to clinicians and pathologists of an earlier era under a variety of names of which acute parenchymatous nephritis or acute tubular nephritis were perhaps the most widely used. He stated that the widespread usage and popularity of the Volhard and Fahr [5] classification of renal diseases which entirely omits mention of acute parenchymatous nephritis, may have been partially responsible for the lapse of interest in, and knowledge of, the syndrome. Be that as it may, there has been a growing realization that this entity, first described in relation to injuries of military origin, is perhaps one of the commoner renal diseases being encountered in a diversity of diseases having little, if any, military connotations.

Even during the past several years, problems of terminology have tended to hinder the full-fledged emergence of this syndrome as a clinical entity. These problems are, perhaps, of more than semantic interest, since variations in nomenclature have often connoted an incomplete understanding of basic mechanisms involved in the production of the syndrome. Thus many essential features of this entity are to be observed in cases of so-called pre-renal azotemia,[6] a concept which often has to be abandoned when the postmortem examination shows organic renal damage. Hemoglobinuric nephrosis, a term used recently by Mallory,[7] tends, perhaps, to emphasize unduly an aspect of the disease which need not always be present in classical examples. Lucké [8] has recently proposed the term, lower nephron nephrosis, for the

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syndrome. This name appears to be already achieving widespread clinical popularity so that its use conjures up a specific syndrome. It possesses the advantage of localizing the renal lesion while at the same time avoiding commitment in the vexed question of the predominance of renal anoxia or various nephrotoxins as the principal etiological factors. Many factors in the etiology still remain obscure as will be observed below.

In addition to the crush syndrome, lower nephron nephrosis has been observed in the following conditions: non-traumatic muscular ischemia,[9] burns,[10] hemolytic transfusion reaction,[11] heat stroke,[12] blackwater fever,[13] toxemias of pregnancy,[14] sulfonamide intoxication,[15] the so-called hepatorenal syndrome,[16] and poisonings with certain vegetable and chemical agents.[17] Two common denominators are present in virtually all of these disease processes, namely, tissue or blood destruction, and shock of varying degree. It is probable that both of these factors operate synergistically to produce the clinical and pathological features of lower nephron nephrosis. The manner in which they do so has been elucidated in recent years by many significant physiological and biochemical investigations. However, before launching into a discussion of these observations, it would be well to present briefly the clinical and pathological features of the syndrome.

In view of the varied etiology it is somewhat difficult to present a single comprehensive clinical picture. Suffice it to say, that after some mishap, involving either extensive tissue injury or destruction, or blood destruction, followed by a transient interval of shock, the patient is observed to become oliguric or even anuric. Such urine as may be passed is highly acid, has a low, fixed specific gravity and may often be bloody, port-wine colored or smoky in appearance. The passage of heme pigmented urine is not universally present. The nature of the pigment, whether it be hemoglobin or myohemoglobin, can usually be ascertained by spectroscopic study. Proteinuria of a moderate degree is usually present and the sediment usually contains granular or pigmented casts. Chemical studies of the blood will reveal a progressive rise in non-protein nitrogen, at times an increase in potassium

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and phosphate, and a decrease in alkali reserve. The blood pressure, after recovery from the initial shock phase, tends to rise to moderate hypertensive levels. Edema is usually insignificant. Most aspects of the uremic syndrome will be observed and in fatal cases death in typical uremic coma is usual. The mortality rate is high. Lucké [8] states it to be approximately 90 per cent, with death occurring anywhere from 2 to 30 days after onset. It must be remembered that most cases hitherto have been observed and managed under what would hardly be called optimal conditions. Those cases which recover, either spontaneously or as the result of correct therapeutic management, begin to show a diuresis which is often characterized by the excessive loss of sodium and chloride in the urine. Ultimately there is a complete return to normal renal function.

The pathological picture encountered in fatal cases is characteristic. The kidneys are swollen and pale. Cross-section reveals widening and pallor of the cortex which stands out in sharp contrast to the medullary zone which is dark and has accentuated striations. The characteristic histopathology is observed in the distal portion of the nephron, involving the epithelium of the thick limb of Henle and the distal convoluted tubules. These areas of the nephron exhibit focal patches of cellular degeneration and necrosis. Some lumina contain casts of a heme compound. There may be moderate edema and cellular reaction in the stroma about the more severely damaged tubules, and adjacent thin-walled veins often exhibit parietal thrombi.

The syndrome of lower nephron nephrosis is encountered commonly in individuals who have managed to survive for some time following a period of sub-lethal shock. Obviously, patients in profound shock will usually die of circulatory failure prior to the development of specific renal pathology, while those only mildly shocked will usually not develop any significant renal damage. It may be rewarding to review briefly some of the fundamental disturbances in renal circulation which accompany shock of varied etiology. The occurrence of shock is accompanied by contraction of the vascular bed by peripheral constriction so that the diminished volume of available blood will be adequate to supply such vital organs as the brain whose function must be maintained to avoid immediate death.[18] In hemorrhagic shock, for example, with severe blood loss, the kidneys are included in the constricted periphery. In time of deficit, they appear to stand intermediate between the skin and muscle which can survive long periods of ischemia, and the central nervous system which can survive almost none.[19] Undue prolongation of the period of deficient blood supply apparently results in organic renal damage of the type described above. Van Slyke [18] conveniently divides the phases of renal failure in shock into an initial, functional, rever-

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[19] Green, H. D., Cosby, R. S., and Lewis, R. N.: Modification of blood flow in skin and muscle of dogs in hemorrhagic shock, Fed. Proc., 1942, i, 32, Part II.

sible phase due primarily to circulatory deficit and a second phase, persisting after recovery from shock, attributable to organic injury, which may or may not be reversible. The duration of shock and renal circulatory impairment is of vital significance. Renal failure, associated with persistent oliguria or anuria after recovery from shock, does not necessarily imply a progressive renal lesion. As a matter of fact, the renal damage may be looked upon as having occurred during the period of shock only. From that time onward the fate of the patient, from a renal standpoint, will depend literally on a race between the progressing azotemia and gradual repair of the renal injury.

There is apparently still some controversy over the mechanism of renal circulatory impairment during shock. According to Van Slyke et al.[18] this is due, primarily, to renal vaso-constriction, their opinion being based upon the observation that renal blood flow, measured by the clearance of para-amino hippurate, is diminished. On the other hand, Trueta et al.[20] have proposed a somewhat different mechanism for the renal ischemia. In a series of experiments on rabbits, they observed that the application of a tourniquet to one of the hind legs for a period of hours resulted in an alteration of the circulation in the homolateral kidney. This was characterized by an apparent increase in renal circulation but only through part of the kidney. There was a bypassing of the renal cortical vascular channels via the medulla. The bypassing seems to occur through what are called the juxtamedullary glomeruli thereby effectively producing cortical ischemia. Ultimate judgment concerning these concepts must, for the time being, be left subjudice. It is fascinating to speculate upon the possibility of the Trueta mechanism as the etiological factor in a related renal syndrome, bilateral symmetrical cortical necrosis, observed in rare instances following shock, in post-partum or post-operative patients.

Since the syndrome of lower nephron nephrosis is observed following a variety of traumata, it is inevitable that the renal pathology be considered as resulting from the action of a nephrotoxin. Critical consideration of the syndrome forces one to tend to adhere to the concept of the primacy of renal anoxia induced by renal circulatory deficit. Nevertheless there is considerable evidence pointing toward the importance of a nephrotoxic agent. A major difficulty in the acceptance of the idea of a nephrotoxin lies in the diversity of these agents. There is still some controversy over the toxicity of free hemoglobin or myohemoglobin. However, the consensus seems to be that solutions of pure hemo- or myohemoglobin[11] are not nephrotoxic. Nephrotoxic effects occurring after injection of these compounds have been attributed to abnormal breakdown products or derivatives such as hematin (sodium ferrihemate).[21] The latter substance also produces intense renal vaso-constriction so that it is somewhat difficult to know whether tubular damage is due to primary cellular injury or is secondary to vaso-constriction.

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[21] ANDERSON, W. A. D., MORRISON, D. B., and WILLIAMS, E. F.: Pathologic changes following injections of ferrihemate (hematin) in dogs, Arch. Path., 1942, xxxiii, 589–602.

Other products of tissue breakdown have also been observed at times to have a nephrotoxic effect. It has been suggested [22] that toxic products liberated from injured tissue are detoxified by the liver if the rate of release into the blood stream is sufficiently slow, but that this mechanism does not operate efficiently with excessive flooding of the circulation.

With the establishment of organic renal damage, oliguria and anuria become cardinal features of the syndrome. There seems to be little doubt that the anuria of the early shock phase is directly related to the fall in arterial pressure below a critical level necessary to maintain glomerular filtration. In the second or renal damage phase several mechanisms may be operative. For many years the rôle of tubular obstruction by heme pigment casts has been the subject of controversy. The weight of evidence seems to be against this as an important factor. Some of the reasons cited include: (1) the number of tubules observed to be obstructed appears to be inadequate to explain failure of excretion of urine; (2) the syndrome can occur in the absence of heme pigment casts; (3) there is little if any dilatation of glomerular spaces and upper segments of the tubule which should be observed with obstruction. Oliver [23] has recently revived interest in the rôle of obstruction as a result of his studies on individually dissected nephrons. It seems likely, however, that a more important mechanism producing oliguria is the unselective reabsorption of glomerular filtrate by damaged tubular epithelium. Richards [24] by direct observation of the living frog's kidney, noted that after poisoning by mercuric chloride even though glomerular filtration remained quite active, no urine could be seen to emerge from the ureters. In other words, there was literally a "leaking" back of filtrate into the blood of the peri-tubular capillaries. The tubular walls, devitalized by poison, approached dead membranes in their behavior. The entire glomerular filtrate, both water and solutes, passed indiscriminately back presumably drawn by the osmotic attraction of the plasma proteins for the filtrate water. The application of this concept to the human kidney of lower nephron nephrosis must still be considered as a tentative rather than a demonstrated explanation for the anuria. It has been suggested also that increased intrarenal pressure, offering abnormal resistance to glomerular filtration, may likewise be a factor in the anuria.[25]

As a result of the recent delineations of the clinical, pathological and physiological features of this syndrome, therapeutic management should offer more hope of success. It is important to maintain, constantly, the concept that this is a self-limited disease which, if survival is achieved, will be followed ultimately by complete recovery of renal function. It is beyond the scope of this brief summation to discuss details of therapeutic manage-

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[24] Richards, A. N.: Direct observations of change in function of renal tubule caused by certain poisons, Trans. Assoc. Am. Phys., 1929, xliv, 64–67.

[25] Peters, J. T.: Oliguria and anuria due to increased intrarenal pressure, Ann. Int. Med., 1945, xxiii, 221.

ment. Nevertheless, certain principles can be stressed: (1) prevention is feasible in regard to certain of the precipitating causes, e.g., hemolytic transfusion reaction, sulfonamide intoxication, etc.; (2) termination of shock as quickly as possible by the use of whole blood, plasma, human albumin solution or other infusion fluids will reduce the period of renal anoxia and thereby diminish organic renal damage; (3) *avoidance of overhydration during the period of oliguria or anuria;* (4) increased use of several methods of treatment still looked upon as in their clinical infancy, e.g., the "artificial kidney," [26] and peritoneal irrigation [27]; (5) careful observation of the serum chloride level during the diuresis phase of recovery so as to circumvent the occurrence of hypochloremia.

The very diversity of the precipitating causes of lower nephron nephrosis virtually insure its frequent clinical occurrence in almost every variety of medical practice. Understanding of many of the basic mechanisms involved has already been achieved and should lead to reduction in mortality.

M. S. S.

[26] KOLFF, W. J., and BERK, H. R. J.: The artificial kidney: a dialyzer with great area, Acta med. Scandin., 1944, cxvii, 121.

[27] FINE, J., FRANK, H. A., and SELIGMANN, A. M.: The treatment of acute renal failure by peritoneal irrigation, Ann. Surg., 1946, cxxiv, 857.

REVIEWS

Psychiatry in a Troubled World: Yesterday's War and Today's Challenge. By WILLIAM C. MENNINGER, M.D. 636 pages; 16 × 24.5 cm. The Macmillan Co., New York. 1948. Price, $6.00.

This is by far the most important book on psychiatry in World War II so far published. The author was, for the major part of the war, Chief Consultant in Neuropsychiatry to the Surgeon General. He describes, with much documentation, the size and characteristics of the task, the errors made, the obstacles encountered and the results achieved. He demonstrates how the lessons learned in World War I were almost completely ignored and forgotten by the Army before World War II. The last part of the book deals with the possible application of lessons learned in the recent War to post-war civilian problems. Because of the extensive uses of source material and bibliography the book will serve as an extremely useful reference book in any study of the applications of psychiatry to military medicine, medical education, criminology, industry and medicine in general.

H. W. N.

Psychobiology and Psychiatry: A Textbook of Normal and Abnormal Human Behavior. 2nd Ed. By WENDELL MUNCIE, M.D. 620 pages; 17 × 25 cm. The C. V. Mosby Co., St. Louis, Mo. 1948. Price, $9.00.

This book is an official and formal exposition of Meyerian psychiatry. It is a textbook "aimed primarily for the use of students." It is recommended as a good description of the teaching of Adolf Meyer. Its biggest weakness, however, is that it ignores the outstanding contributions made to modern dynamic psychiatry by various workers in the field of psychoanalysis.

H. W. N.

Mental Mischief and Emotional Conflicts. Psychiatry and Psychology in Plain English. By WILLIAM S. SADLER, M.D., F.A.P.A., Chicago. 396 pages; 16 × 24 cm. The C. V. Mosby Co., St. Louis, Mo. 1947. Price, $6.00.

Even if Dr. Sadler's book were written, as claimed, in "plain English," the reviewer still would recommend it neither to the layman nor professional reader. The concepts offered are not in keeping with present-day psychiatric thinking. His personal opinions regarding etiology, mental mechanisms and therapy are neither scientific, sound nor practical in the reviewer's opinion.

H. W. N.

Symposium on Medicolegal Problems, under the Co-Sponsorship of the Institute of Medicine of Chicago and the Chicago Bar. Edited by SAMUEL S. LEVINSON for the Committees of the Institute of Medicine and the Chicago Bar Association. 255 pages; 13 × 20 cm. J. B. Lippincott Co., Philadelphia. 1948. Price, $5.00.

This small book represents a praiseworthy effort on the part of the Chicago Bar Association and the Chicago Institute of Medicine to bring some order into the chaos of medicolegal work. The method of presentation is that of a symposium. First doctors and then lawyers discuss each problem from their respective viewpoints. The ensuing general discussion and questions are faithfully transcribed. All of the speakers are men of undisputed ability in their respective fields. Among the important problems discussed are expert testimony, artificial insemination, medicolegal pathology, sterilization and scientific tests in evidence.

The method of presentation is subject to the unevenness and personal bias that typify any group discussion but it serves to bring into form various points of conflict between medical and legal minds. Probably such differences in outlook can never be entirely settled, as the legal emphasis on absolute truth and on precedent is so fundamentally different from the medical stress on the working hypothesis and the reserving of judgment. It is only through such joint discussions as this book records that mutual understanding if not agreement may be achieved.

There is much in this volume both of stimulus and of helpful information for any physician doing medicolegal work.

H. J. M.

A Textbook of Clinical Neurology. 2nd Ed., Revised. By J. M. NIELSEN, M.D., F.A.C.P. 699 pages; 18.5 × 26 cm. Paul B. Hoeber, Inc., New York. 1946. Price, $7.50.

This book of neurology has been written especially for the student and the general practitioner. It can be used as an introduction to neurology as well as a brief reference book. Neurological diseases are discussed in this text in a neuroanatomical order, such as diseases of the peripheral nerves, spinal cord, cranial nerves, brain stem, cerebellum, thalamus, basal ganglia and cerebrum. There are individual sections related to epilepsy, migraine, trauma to the brain and the spinal cord, degenerative diseases, idiocy, congenital diseases, avitaminosis as well as a chapter on the psychoneuroses. There is a chapter devoted to the fundamentals of electroencephalography. Each chapter has an adequate, up-to-date bibliography. The chapter on inflammations and intoxications is very well written. The book is brief, well written and contains many plates and diagrams which are better than average.

W. L. F.

Urologic Roentgenology. 2nd Ed., Revised. By MILEY B. WESSON, M. D., Ex-President, American Urological Association. 259 pages; 24 × 15.5 cm. Lea & Febiger, Philadelphia. 1946. Price, $5.50.

The author's aim to provide a *vade mecum,* rather than a treatise, has been faithfully accomplished. As an introduction to this specialized field this volume will be very welcome.

The material is presented in a factual manner and yet warnings are interjected to impress the reader that radiological evidence alone must be supplemented and corroborated by clinical study before a final diagnosis is accepted. Perhaps these warnings could have been repeated more often by the author.

The radiological findings and differential diagnoses are well presented. All the illustrations are excellent. A well chosen bibliography is furnished at the end of each chapter.

H. D. V.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Correlative Neuroanatomy. 4th Ed. By JOSEPH J. MCDONALD, M.S., M.Sc.D., M.D., JOSEPH G. CHUSID, A.B., M.D., and JACK LANGE, M.S., M.D. 156 pages; 25 × 17.5 cm. (loose-leaf, paper-bound). 1948. University Medical Publishers, Palo Alto, California. Price, $3.00.

A Course in Practical Therapeutics. By MARTIN EMIL REHFUSS, M.D., F.A.C.P., Professor of Clinical Medicine and Sutherland M. Prevost Lecturer in Therapeutics, The Jefferson Medical College, Philadelphia, etc.; F. KENNETH ALBRECHT, M.D., Formerly Clinical Director U. S. Marine Hospital, Baltimore, etc., and ALISON HOWE PRICE, A.B., M.D., Asst. Professor of Medicine, The Jefferson Medical College, Philadelphia, etc. 824 pages; 29 × 22.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $15.00.

Diseases of the Ear, Nose and Throat. By WILLIAM WALLACE MORRISON, M.D., Professor of Otolaryngology and Attending Otolaryngologist, New York Polyclinic Medical School and Hospital, etc. 772 pages; 24.5 × 16 cm. 1948. D. Appleton-Century Company, Inc., New York. Price, $8.50.

"Elective Alimentary Rest" and the Elimination of So-Called "Paralytic Ileus" after Abdominal Operations. By V. J. KINSELLA, M.B., Ch.M. (Syd.), F.R.C.S., F.R.A.C.S. 35 pages; 21.5 × 14 cm. (paper-bound). 1948. Angus & Robertson, Ltd., Sydney, Australia. Price, 3/.

General Endocrinology. By C. DONNELL TURNER, Ph.D., Associate Professor of Zoology at Northwestern University. 604 pages; 24.5 × 16 cm. 1948. W. B. Saunders Company, Philadelphia. Price, $6.75.

Give Them a Chance to Talk: Handbook on Speech Correction for Cerebral Palsy. By BERNEICE R. RUTHERFORD. 116 pages; 23 × 15 cm. (paper-bound). 1948. Burgess Publishing Company, Minneapolis. Price, $2.75.

Hemolysis and Related Phenomena. By ERIC PONDER, The Nassau Hospital, Mineola, New York. 398 pages; 24 × 15.5 cm. 1948. Grune & Stratton, Inc., New York. Price, $10.00.

How Laymen Cut Medical Costs. 35 pages; 22.5 × 15 cm. 1948. Public Health Institute, Chicago. Distributed without cost.

Investigations on Agonal Acidosis. By IB FABRICIUS HANSEN. 135 pages; 26.5 × 18.5 cm. (paper-bound). 1948. Povl Branner, Copenhagen, Denmark. Price, $3.00.

The Mechanism of Abdominal Pain. By V. J. KINSELLA, M.B., Ch. M. (Syd.), F.R.C.S. (Eng.), F.R.A.C.S., Hon. Surgeon, St. Vincent's Hospital, Sydney, etc. 230 pages; 25.5 × 15 cm. 1948. Angus & Robertson, Ltd., Sydney, Australia. Price, 32/6.

Practice of Allergy. 2nd Ed. By WARREN T. VAUGHAN, M.D., Richmond, Virginia. Revised by J. HARVEY BLACK, M.D., Dallas, Texas. 1132 pages; 26.5 × 17.5 cm. 1948. The C. V. Mosby Company, Saint Louis. Price, $15.00.

Racial Variations in Immunity to Syphilis: A Study of the Disease in the Chinese, White, and Negro Races. By CHESTER NORTH FRAZIER and LI HUNG-CHIUNG. 122 pages; 23.5 × 15.5 cm. 1948. The University of Chicago Press, Chicago. Price, $2.50.

Roentgen Studies of the Lungs and Heart: A Series of Lectures Delivered at the Center for Continuation Study, University of Minnesota. By NILS WESTERMARK, M.D., Director, Department of Radiology, St. Göran's Hospital, Stockholm, Sweden. Edited by LEO G. RIGLER, M.D., Professor of Radiology, University of Minnesota. 216 pages; 27 × 17.5 cm. 1948. University of Minnesota Press, Minneapolis. Price, $7.00.

The Skull, Sinuses and Mastoids: A Handbook of Roentgen Diagnosis. By BARTON R. YOUNG, M.D., Professor of Radiology, Temple University Medical School. 328 pages; 21 × 14.5 cm. 1948. The Year Book Publishers, Inc., Chicago. Price, $6.50.

Treatise on Surgical Infections. By FRANK LAMONT MELENEY, M.D., Associate Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University, etc. 713 pages; 24.5 × 16 cm. 1948. Oxford University Press, New York. Price, $12.00.

Twentieth Century Speech and Voice Correction. Edited by EMIL FROESCHELS, M.D., President, International Society for Logopedics and Phoniatrics, etc. 321 pages; 21.5 × 14 cm. 1948. Philosophical Library, New York. Price, $6.00.

Venous Thrombosis and Pulmonary Embolism. By HAROLD NEUHOF, M.D., Clinical Professor of Surgery in Columbia University, etc. 159 pages; 26 × 17.5 cm. 1948. Grune & Stratton, Inc., New York. Price, $4.50.

COLLEGE NEWS NOTES

Research Fellowships—The American College of Physicians

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1949–June 30, 1950. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for proper pursuit of his work. The stipend will be from $2,200 to $3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1948. Announcement of the awards will be made as promptly as is possible.

A.C.P. Postgraduate Courses

Autumn, 1948

The Preliminary Bulletin of Postgraduate Courses, published early in July, presented the calendar and description of the eight courses arranged by the American College of Physicians between August and December, 1948. Course No. 1, "Cardiology," at the National Institute of Cardiology, Mexico, and Course No. 2, "Internal Medicine with Emphasis on Pathological Physiology," at the University of Cincinnati, have been concluded, the latter course with maximum registration. Course No. 3, "Internal Medicine," at the University of Pittsburgh, is in progress, with a large registration (limited to 50).

Course No. 6, "Recent Advances in the Diagnosis and Treatment of Cardiovascular Disease," at the Massachusetts General Hospital, Boston, November 15–24, has been filled to capacity since the middle of August.

At the time of the preparation of this announcement, August 15, accommodations are still available in the following courses:

No. 4, "Internal Medicine"
University of Michigan Medical School
Ann Arbor, Mich.
Dr. C. C. Sturgis, Director
One Week—October 18–29

No. 5, "Endocrinology"
University of Illinois College of Medicine (classes meeting at the LaSalle Hotel, Chicago)
Chicago, Ill.
Dr. Willard O. Thompson, Director
One Week—November 1–6.

No. 7, "Cardiovascular Disease"
Emory University School of Medicine
Atlanta, Ga.
Dr. R. Bruce Logue, Director
One Week—December 6–11

No. 8, "Gastro-enterology"
Graduate Hospital of the University of Pennsylvania
Philadelphia, Pa.
Dr. Henry L. Bockus, Director
One Week—December 6–11

All inquiries should be addressed to the Executive Secretary, American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa.

Regular Autumn Meeting, Board of Regents

The regular autumn meeting of the various committees and of the Board of Regents will be held at Philadelphia, November 5, 6 and 7.

The Committee on Nominations will meet Friday, November 5; the Committe on Credentials, November 5 and 6; all other committees, on November 6; the Board, on November 7. Proposals of candidates for membership in The College must be filed sixty days in advance of action. Next succeeding meetings of the Committee on Credentials will be held in late February and on March 26, 1949.

The American College of Physicians has added to its roster of Life Members the names of Jacob L. Tuechter, M.D., F.A.C.P., Cincinnati, Ohio, and Gilbert E. Brereton, M.D., F.A.C.P., Dallas, Tex. The endowment funds of the College have been augmented by their subscriptions to Life Membership.

Contributions to the College Library

Grateful acknowledgment is made of the kindness of Franklin H. Top, M.D., F.A.C.P., Detroit, Mich., who recently gave to the College Library of Publications by Members a copy of his new 2nd Edition of the "Handbook of Communicable Diseases," published by The C. V. Mosby Company, St. Louis, 1947.

Acknowledgment is made also of receipt of the Handbook of the Royal College of Physicians and Surgeons of Canada, and of copies of the Annual Lectures of that College for 1947, sent through the kindness of J. E. Plunkett, M.D., F.A.C.P., Ottawa, Honorary Secretary of the Royal College. A.C.P. Fellows listed in the Handbook as officers and Council members include: Dr. D. Sclater Lewis, Montreal, Vice President; W. F. Connell, Kingston, H. K. Detweiler, Toronto, Ray F. Farquharson, Toronto, Richard Lessard, Quebec, and A. G. McGhie, Hamilton, members of the Council representing the Division of Medicine.

American Board of Internal Medicine

Revision, July 1, 1948

Memorandum to Applicants for Admission to Examination

In the November, 1947, issue of the Annals of Internal Medicine, Volume 27, No. V, page 845, appeared the revised memorandum to applicants for admission to the examinations of the American Board of Internal Medicine. Further revisions have now taken place as of July 1, 1948, and are hereunder published.

I. *General Qualifications*

C. Change to read as follows:
All candidates must be active members in good standing in their County and State medical societies in the state of legal residence. Under unusual and exceptional circumstances the Board reserves the privilege of modifying this requirement.
(This ruling shall not apply to commissioned officers of the United States regular Army or Navy or United States Public Health Service who are otherwise members of the American Medical Association.)

II. *Professional Qualifications*

I. The Board will grant one year of graduate training credit, or one year in satisfaction of the requirements of practice, regardless of assignment, for active duty as a commissioned officer in the United States Army, Navy, or United States Public Health Service for one year or more, beginning on or subsequent to December 7, 1941 and terminating on or before January 1, 1947. Commissioned officers serving less than one year prior to January 1, 1947 may apply that interval as graduate training.

Application

Paragraph 3

The application must be accompanied by one recent, signed photograph of the candidate mounted on the application, and the registration and examination fee of forty dollars, which fee will cover both the written and oral examinations. An additional fee of ten dollars will be required when the certificate is issued.

Method of Examination

Paragraph 1

. . . The written examination is held simultaneously in different sections of the United States and Canada on the third Monday of October of each year.

Re-examination

Paragraph 3

. . . A fee of twenty dollars is required for each additional oral examination.

Paragraph 4

Candidates who have taken one written examination or one oral examination while on active duty overseas as a commissioned officer in the United States Army, Navy, or Public Health Service will be authorized to take a fourth written examination or a fourth oral examination if necessary. This regulation will not apply to candidates in the Armed Forces who took their written or oral examinations in the United States.

THE AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY

"In order to facilitate the arrangements for training in child psychiatry (which constitutes a major aspect of modern psychiatry), the American Board of Psychiatry and Neurology will accept one year of training in psychiatric clinics for children which may or may not be a part of a hospital approved for residency training, provided such a clinic gives adequate supervision and instruction for full-time training during the entire third year of the required three-year formal training period. For the purpose of evaluating such clinics, the following conditions and criteria are deemed essential by the American Board of Psychiatry and Neurology:

1. That the clinic have a full-time medical director, psychologist, and social worker qualified by training and experience in child psychiatry and allied fields to supervise the training of residents;
2. That the major portion of such training be devoted to therapy adequately supervised by this qualified staff;
3. That the service and teaching activities of the clinic be integrated with those of the community and its social agencies;
4. That clinic work be supplemented by seminars, case conferences, journal clubs or other opportunities for the discussion of the basic principles involved in outpatient work with children and parents, teacher, public health and welfare agency personnel;
5. That such a training clinic be well established in the community with a qualified staff that has operated together long enough as a team to insure stable and sound functioning;
6. That the senior members of the clinic team show evidence of previous experience in the teaching of psychiatry in general, child psychiatry in particular, and their allied fields.

"These criteria set forth by the Board pertain more particularly to community-sponsored clinics offering full-time training in child psychiatry during the third year of formal residency training. If these clinics are affiliated with hospitals already maintaining approved programs, separate approval is not required unless warranted on the basis of their meeting all requirements for straight fellowship training in child psychiatry.

"The following clinics are acceptable to the American Board of Psychiatry and Neurology as qualifying under these provisions:

Clinic	*Director*
Children's Psychiatric Division, Langley Porter Clinic, San Francisco, California.	Dr. Stanislaus Szurek
Bureau of Mental Hygiene, 1179 Main Street, Hartford, Connecticut.	Dr. Jas. M. Cunningham
Louisville Mental Hygiene Clinic and Child Study School, 610 South Floyd Street, Louisville, Kentucky.	Dr. Spafford Ackerly
The Guidance Center, 1737 Prytania Street, New Orleans, Louisiana.	Dr. Milton E. Kirkpatrick
The Psychiatric Clinic of the Mental Hygiene Society of Maryland, Baltimore, Maryland.	Dr. H. Whitman Newell
Children's Center, 244 Townsend Street, Roxbury, Massachusetts.	Dr. Marian Putnam and Mrs. Beata Rank, co-directors
Judge Baker Guidance Center, 38 Beacon Street, Boston, Massachusetts.	Dr. George E. Gardner
Amherst H. Wilder Clinic, 379 Rice Street, St. Paul, Minnesota.	Dr. Hyman S. Lippman
Central Clinic, Cincinnati General Hospital, Cincinnati, Ohio.	Dr. Maurice Levine
Child Guidance Center, 1711 Fitzwater Street, Philadelphia 46, Pennsylvania.	Dr. Frederick H. Allen
Pittsburgh Child Guidance Clinic, 3004 Victoria Street, Pittsburgh 13, Pennsylvania.	Dr. Harry M. Little
Children's Service Center of Wyoming Valley, 335 South Franklin Street, Wilkes-Barre, Pennsylvania.	Dr. J. Franklin Robinson

American College of Chest Physicians Offers Postgraduate Course

The American College of Chest Physicians has announced its first annual postgraduate course presenting the newer aspects of diseases of the chest at the Hotel New Yorker, New York City, November 8 to 12, 1948. Applications for the course should be addressed to their Executive Offices, 500 North Dearborn Street, Chicago 10, Ill.

Continuation Course in Diseases of the Digestive Tract

The Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation, 2020 E. 93rd St., Cleveland 6, Ohio, has scheduled a continuation course in Diseases of the Digestive Tract to be given at the Cleveland Clinic Building on Thursday, Friday, and Saturday, October 7, 8, and 9, 1948. Among guest teachers, other than members of the Clinic staff, are Dr. Lester R. Dragstedt, F.A.C.P., Chicago, Illinois, and Dr. T. Grier Miller, F.A.C.P., Philadelphia, Pennsylvania. Dr. Edwin P. Jordan, F.A.C.P., is the Director of Education of the Institute.

American Academy of Allergy Orientation Course in Allergy

The American Academy of Allergy has announced an Orientation Course in Allergy, to be given during the week of October 25 to 29, inclusive, 1948, at Northwestern University Medical School. Inquiries should be addressed to Samuel M. Feinberg, M.D., Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill.

Graduate Instructional Course in Allergy

An intensive graduate instructional course in allergy will be presented by The American College of Allergists under the auspices of the University of Oregon Medical School, Portland, Oregon, November 8 to 12, 1948, inclusive. Hotel headquarters will be at the Heathman Hotel. The Course includes all phases of the subject and will be represented by specialists in the fields of the basic sciences, as well as specialists in allergy, detailing treatment and management of the allergic patient. There will be panel discussion and demonstrations of technics. Printed comprehensive abstracts of the lectures are furnished the registrants. The Course is available to members and non-members of the College. Applications should be placed with Dr. Fred W. Wittich, Secretary, 423 La Salle Medical Building, The American College of Allergists, Minneapolis 2, Minnesota. Programs will be mailed upon request. The charge for the Course is $75.00 payable at the registration desk.

The American Public Health Association will hold its 77th Annual Meeting in New York City during the week of October 23, 1949. Its 76th Annual Meeting will be held in Boston, November 8 to 12, 1948.

The 1949 Assembly of the Interstate Postgraduate Medical Association of North America will be held in Philadelphia, Pa., the week of October 31, 1949.

Regional Meeting on Disaster Preparedness Held at Philadelphia

Representatives from surrounding States and the District of Columbia attended a special meeting on Disaster Preparedness at The Philadelphia County Medical Society on June 8, the purpose of the Conference being to formulate a uniform plan

of organization to provide emergency medical care in the event of an atomic disaster.

Dr. Perrin H. Long, member of the A.M.A. Emergency Medical Council, and at present assigned to the Office of Atomic Warfare in Washington, reported on plans being formulated to cope with any atomic disaster. Technical sections are being planned for transportation, disasters, policing, fire control, engineering, chemical and biological warfare, radiologic defense and medicine. The medical section will be divided into the Public Health Service, the Administration Service and the Medical Care Service. Under the Public Health Service will fall conveniences which are normal in any large city within the Department of Health, such as protection of food, milk and water. The Administration Service will be concerned with hospitalization and evacuation problems. The Medical Care Service will include physicians and persons in allied fields to take care of the ill and injured. It is planned to create eight technical mobile groups, which can be moved speedily to disaster scenes. Physicians will be evaluated, so that their professional abilities may be used to the best advantage. It is anticipated that a definite program will be evolved in Washington.

Need for Internists in Veteran Administration Hospitals

Branch Office No. 5 of the VA, Atlanta 3, Ga. appeals to the internists of the United States to help them staff the 17 hospitals under their jurisdiction. There are abundant opportunities for physicians who are qualified in internal medicine and the subspecialties to head services and sections in these hospitals which are located throughout the southeast from Johnson City, Tennessee to Tuscaloosa, Alabama, and from Memphis, Tennessee to Coral Gables, Florida.

In addition to openings for specialists, there are also abundant opportunities for young men who have finished their residency training, and who now need two or more years of preceptorship training, under certified internists, with teaching ability, where they may make their final preparation in an academic atmosphere for completion of the American Board requirements.

The organization plan of all of our hospitals follows the outline prepared by the Council on Medical Education and Hospitals published by the American Medical Association (Jr. Am. Med. Assoc., 1939, cxiii, 794). Emphasis is placed on bedside instruction, teaching rounds, seminars, clinical-pathological conferences, demonstrations and lectures. All of our hospitals are affiliated with nearby medical schools for educational purposes and twenty qualified Branch Consultants, covering every specialty in Medicine and Surgery, pay periodic visits to the hospitals for teaching and supervision of the professional service in their respective fields.

All of our hospitals possess large well-equipped laboratories and libraries. All new modern textbooks and an average of 100 current journals are available to the staff doctors. Opportunities for research and study are splendid. Every possible consideration is given to the encouragement and stimulation of clinical investigation and professional advancement. Attendance at conventions and postgraduate courses is approved on official leave. Excellent bibliographical and medical illustration service is available to all of our doctors upon request.

Salaries, while they are not high, the upper limit being $11,000.00 per year, are adequate for those physicians who are interested primarily in professional advancement, an opportunity to contribute to the medical literature, or who have an overwhelming desire to practice top-flight medicine in an atmosphere of professional freedom.

There are other advantages to participation in the new Department of Medicine and Surgery of the VA including 30 days of annual leave and retirement privileges, but the greatest inducement of all is the ability to practice first class medicine without being hampered by the inevitable consideration of the cost of medication, special examinations and laboratory procedures, consultation service or lengthy hospitalization.

such as inevitably affects the character of professional services rendered by the civilian physician in private practice. Satisfaction in the splendid service rendered to worthy veterans and their heartfelt gratitude expressed to the physician undoubtedly plays a great part in the professional morale so high in our hospitals. There has been a great improvement in every phase of hospital service since the renaissance spearheaded by Dr. Paul R. Hawley and promoted, expanded, and brought into full-flower through the efforts of our present Chief Medical Director, Dr. Paul B. Magnuson.

Present openings in our hospital are as follows:

1. Chief of Medical Service, Montgomery VA Hospital; 300-bed general medical and surgical hospital, located in the city of Montgomery, Alabama; population of 110,000 people. We also need seven other younger internists at this hospital. This is the only general VA Hospital in the State of Alabama, and the clinical material is excellent for teaching and research. The educational program in this hospital is carried on under the auspices of the University of Alabama Medical School.

2. Chief of Medical Service, Dublin, Georgia. This is the former Naval Hospital located about 45 miles from Macon, Georgia. This hospital has just been opened and for the time being is functioning as a 200-bed general hospital. The educational program in this hospital will be carried on under the auspices of Emory University Medical School.

3. Chief of Medical Service, Murfreesboro, Tennessee; 900-bed Neuropsychiatric Hospital with small general medical and surgical unit. The Chief of Service would serve as a consultant to the other services and could, if acceptable to the Dean's Committee, also serve as a part-time teacher at Vanderbilt University in Nashville, some 32 miles from Murfreesboro. The educational program at this hospital is being carried on under the auspices of Vanderbilt University Medical School.

4. Chief of Medical Service, Mountain Home, Tennessee. We have six openings for internists interested in training in the various subspecialties of Internal Medicine under the supervision of two certified specialists in the hospital located at Mountain Home near Johnson City, Tennessee. The educational program carried on in this hospital is under the auspices of Bowman-Gray Medical School, Winston-Salem, North Carolina.

5. We have four openings for medical residents at our VA Hospital, Coral Gables, Florida.

6. We also have vacancies for 17 additional internists throughout the Branch and the following specialists:

Orthopedic Surgeons	3	
Anesthesiologists	7	
X-ray Specialists	6	
Otolaryngologists	2	
Pathologists	5	
Physical Medicine	5	
Diseases of the Chest	8	
Psychiatrists	24	
Residents	12	(openings in NP, Radiololgy, Pathology, and Anesthesiology

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At the Annual Meeting of the American College of Radiology, held in Chicago in June, 1948, Dr. E. P. Pendergrass, F.A.C.P., Philadelphia, was elected president for the 1948–49 year, and Dr. J. Edwin Habbe, F.A.C.P., Milwaukee, was elected to the Board of Chancellors.

Robert H. Williams, M.D., F.A.C.P., formerly Associate Professor of Medicine in the Harvard Medical School, became Professor of Medicine and executive officer of the department in the University of Washington School of Medicine on July 1.

Dr. Tinsley R. Harrison, F.A.C.P., Dallas, Tex., has succeeded Arlie R. Barnes, M.D., F.A.C.P., Rochester, Minn., as president of the American Heart Association.

George C. Turnbull, F.A.C.P., Evanston, Ill., has been appointed Attending Physician to the Cook County Hospital, as of July 1.

Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn., was recently elected president of the newly organized Connecticut Diabetes Association. Membership in this society will include physicians, members of allied professional groups, diabetics and their relatives, and those otherwise interested in the control of the disease. One of the principal efforts of the society will be the development of an educational program.

Anthony C. Cipollaro, M.D., F.A.C.P., New York, N. Y., was elected Chairman of the Section on Dermatology and Syphilology of the American Medical Association during the recent Chicago meeting. He was also recently appointed Professor and attending dermatologist and syphilologist in the New York Polyclinic Medical School and Hospital.

Dr. Sidney W. Jennes, F.A.C.P., Waterbury, Conn., was elected the first president of the Connecticut State Allergy Society, which held its first meeting during the recent annual meeting of the Connecticut State Medical Society.

Dr. John W. Shuman, Sr., F.A.C.P., Santa Monica, Calif., has been made an Honorary Fellow of the American Geriatrics Society.

Kenneth M. Smith, M.D., F.A.C.P., accepted full-time appointment in August with the Veterans Administration as Chief of Medicine and Acting Chief of Tuberculosis for Michigan, Ohio and Kentucky. Dr. Smith will retain his appointment in the Ohio State University as Assistant Professor of Medicine. His office will be at 52 S. Starling St., Columbus 8, Ohio.

Dr. Harold Swanberg, F.A.C.P., Quincy, Ill., Editor of the Mississippi Valley Medical Journal, has set up an irrevocable trust known as the Swanberg Kiwanis Foundation, "to sponsor, undertake, or aid in one or more things of a charitable, scientific, literary, or education nature," the trust to be administered by nine trustees, at least one of whom must be a physician. Dr. Swanberg has twice served as president of the Kiwanis Club of Quincy.

Dr. James A. Brussel (associate), Assistant Director of the Willard State Hospital, has been awarded first and second prizes in the 1948 national contest of the American Physician's Literary Guild, which was held in conjunction with the A.M.A. convention in June.

OBITUARIES

DR. GUY WILLIAM WELLS

Guy William Wells, M.D., a Fellow of the American College of Physicians since 1931, died in Providence, R. I., on June 15, 1948, in his 57th year.

A native of Pennsylvania, Dr. Wells received his college and medical education at Brown University and Cornell University Medical College. After an internship at the Rhode Island Hospital and a residency in Medicine at the Peter Bent Brigham Hospital, he entered the practice of internal medicine in Providence and thereafter made his home in that city. He rose to a position of medical leadership in his community and, during the last two years of his life, served as Chief of the Medical Service in both the Pawtucket Memorial and the Rhode Island Hospitals. Dr. Wells devoted much time to the work of his local and state medical societies. From 1936 to 1941, he served as Secretary to the Rhode Island Medical Society and, during 1947, was President of the Providence Medical Association. Both before and after World War II, he was the member from Rhode Island to the House of Delegates of the American Medical Association.

At heart a deeply patriotic citizen, Dr. Wells early in his career joined the Medical Reserve Corps of the U. S. Army, rising to the rank of Major, and in July, 1941, was called to active duty. Following assignments as Chief of the Medical Service of the Station Hospital, Camp Devens, Mass., and on procurement duty for medical officers in Rhode Island, he became Commanding Officer of the 52nd Station Hospital. His unit was among the first to land in North Africa after the invasion, and its record throughout the African and the subsequent Italian campaigns was one of outstanding merit. A tribute to Dr. Wells' service and patriotism was made in the following messages sent by two of his superior officers on learning of his death:

From General Mark Clark:

> . . . His unselfish devotion to duty during our campaigns in Italy endeared him to us all. Together with his countless friends I salute the passing of a loyal soldier and a real friend to man. . . .

From Brig. Gen. J. J. Martin, (M.C.), U.S.A.:

> . . . American medicine and particularly the Army, which he loved so much, have lost a pillar of strength which can never be replaced. As a doctor, a military leader, and a gentleman he had no peer. The many thousands of his comrades who were carried through the trying days of the last war by his unfailing cheerfulness and his uncanny ability to lead the way to the best horizons will bear into eternity the mark of his presence. . . .

Guy Wells was a man of wide popularity with a genuine capacity for friendship. He was conspicuously a gentleman, endowed with tolerance and consideration for the feelings of others. He was by nature a clinician and in practice a very thoughtful and practical doctor. In his positions of leadership it was invariably his way to seek counsel from those under him and to make them feel they shared leadership with him. His death at the peak of his active career is keenly felt by all of his friends, associates and contemporaries.

MARSHALL N. FULTON, M.D., F.A.C.P.

DR. CHARLES CAMILLE DE GRAVELLES

Dr. Charles Camille de Gravelles, F.A.C.P., of New Iberia, La., died on March 22, 1948, of coronary occlusion, at the age of 65. A graduate of the Tulane University of Louisiana School of Medicine in 1910, Dr. de Gravelles achieved prominence in the medical circles of his native state of Louisiana early in his career, and

was known to everyone as a capable, conscientious and highly ethical practitioner. He was president of the Louisiana State Medical Society in 1943, and was elected to Fellowship in the American College of Physicians in 1930. By his death the medical profession of Louisiana loses one of its most distinguished members.

EDGAR HULL, M.D., F.A.C.P.,
Governor for Louisiana

COLONEL GEORGE DAVIES CHUNN

George D. Chunn, a Fellow of the American College of Physicians since 1927, died at Tampa, Fla., March 12, 1948, at the age of 59. A graduate of the University of Arkansas and of the Johns Hopkins University School of Medicine, Dr. Chunn entered the Medical Corps of the U. S. Army in 1914. Among his assignments were posts of Chief of Medical Service of the Station Hospitals at Fort Leavenworth, Kans. and Fort Bragg, N. C. He also served as Commanding Officer of Station Hospital No. 2 at Fort Bragg. Dr. Chunn retired from the service in October, 1945.

Dr. Chunn was a diplomate of the American Board of Internal Medicine, a fellow of the American Medical Association, and a member of The Association of Military Surgeons of the United States.

DR. HENRY SNURE

Dr. Henry Snure died at his home in Los Angeles, Calif., on May 17, 1948. He was born at Lakefield, Minn., November 4, 1887, and obtained his preliminary education at Concordia College, St. Paul. In 1910 he was graduated from the University of Louisville School of Medicine and he practiced in Ohio and Michigan until 1916 at which time he came to California.

During World War I, Dr. Snure served at the United States Naval Hospital, Mare Island, as pathologist. Since that time he had limited his practice to radiology and was for many years the roentgenologist for the California, and California Babies' and Children's Hospitals in Los Angeles. He was a Diplomate of the American Board of Radiology and a Fellow of the American College of Radiology. He became a Fellow of the American College of Physicians in 1929. He served as a Councilor for the Los Angeles County Medical Association for many years and was granted retired membership in this Association in December, 1945.

Dr. Snure was a kindly man and was always willing to help members of the profession with difficult problems. He will be greatly missed in Los Angeles.

LELAND HAWKINS, M.D., F.A.C.P.,
Governor for Southern California

DR. JOHN BARR McALISTER

John B. McAlister, Harrisburg, Pa., died on July 22, 1948. Born in Carroll County, Md., in 1864, Dr. McAlister attended Gettysburg College which he later served as Trustee, and the University of Pennsylvania School of Medicine, from which he received his medical degree in 1877. He served the Harrisburg Hospital for many years as Visiting Physician and as Medical Director. Following his retirement, he was appointed an Honorary Life Member of the staff of that hospital.

Dr. McAlister was a former president of the Harrisburg Academy of Medicine, Dauphin County Medical Society, and the Medical Society of the State of Pennsylvania. He was elected a Fellow of the American College of Physicians in 1926.

DR. EDWIN JACOB SCHISLER

Dr. Edwin Jacob Schisler, F.A.C.P., St. Louis, Mo., died January 12, 1948. He was born at St. Louis in 1874. He received his medical degree from Beaumont Hospital Medical College, later the St. Louis University School of Medicine, in 1896. During his early career, he was Associate in Medicine at St. Louis University School of Medicine and filled various appointments on the staffs of Alexian Brothers Hospital, the Lutheran Hospital, St. Louis City Hospital, and in later years was Consulting Physician to the Alexian Brothers, St. Anthony's and St. John's Hospitals. For several years he was Physician to the Evangelical Deaconess Home and Hospital. He was a Diplomate of the American Board of Internal Medicine, and had been a Fellow of the American College of Physicians since 1923.

DR. ALEXANDER V. GRISWOLD, SR.

Dr. Alexander Viets Griswold, Sr., of Louisville, Ky., died suddenly in his 86th year, on June 22, 1948.

A graduate in 1886 of the University of Louisville School of Medicine, Dr. Griswold interned in the Bellevue Hospital and the Louisville City Hospital, and practiced general medicine in Louisville to the day of his death.

An Associate of the American College of Physicians by virtue of membership in the old American Congress on Internal Medicine, Dr. Griswold was one of the first physicians from Louisville to become a member of that organization, in 1917.

DR. ROBERT HUGH McDONALD

Robert Hugh McDonald, M.D., F.A.C.P., died at his home in Cleveland, Ohio, Sunday, July 20, 1947, from an attack of coronary thrombosis. At the time of his death he was a staff member of the Department of Medicine of the Cleveland Clinic.

Dr. McDonald was born in Oxford County, Ontario, Canada, on October 19, 1895. He attended the University of Toronto Faculty of Medicine, where he was an honor student throughout his course and won the Gold Medal when he obtained the degree of M.B. in 1922. During the following three years, he was a house officer in the Toronto General Hospital. Dr. John Phillips brought him to Cleveland where he spent his remaining years as a member of the Cleveland Clinic staff.

Elected a Fellow of the American College of Physicians in 1939, Dr. McDonald was an active member of The Academy of Medicine of Cleveland, Cleveland Medical Library, American Medical Association, and College of Physicians and Surgeons of Ontario.

In his work in the diagnostic clinic, Dr. McDonald developed a broad knowledge of the entire field of internal medicine; his chief interest, however, lay in diseases of the kidney. An earnest and conscientious worker, he endeared himself to his patients and associates.

Dr. Russell L. Haden, M.D., F.A.C.P.

DR. FRANK JAMES ROHNER

Frank James Rohner, M.D., F.A.C.P., died at his home in Iowa City, Iowa, on July 1, 1947, after an illness of several years. He was born at Carroll, Iowa, July 11, 1882. He received his M.D. degree at the State University of Iowa School of Medicine in 1912. He subsequently served that School as Lecturer in Medicine, 1915–20, Assistant Professor of Medicine, 1920–26, and Associate Professor of Medicine, 1926–27. He then engaged in private practice in Iowa City.

Dr. Rohner was a member of Alpha Omega Alpha, Johnson County and Iowa State Medical Societies, Central Society for Clinical Research, and a Fellow of the American Medical Association. He became a Fellow of the American College of Physicians in 1931.

Dr. Rohner was extremely popular as a teacher, and was regarded by his colleagues and students as an unusually capable clinician. Until his health failed he was in demand as a consultant over a large part of his State. His unfortunate illness removed him from the practice of medicine when he had barely reached his prime. He will long be remembered by his many students and associates as a keen diagnostician and an inspiring teacher and friend.

B. F. WOLVERTON, M.D., F.A.C.P.,
Governor for Iowa

DR. STEPHEN SMITH

Stephen Smith, M.D., F.A.C.P., died suddenly of coronary thrombosis at his home in Pasadena, Calif., on June 3, 1947. His loss was felt deeply by his numerous patients and his colleagues.

Dr. Smith was born at Ellicottville, N. Y., in 1880. He attended the University of Michigan, where he majored in Organic Chemistry under Dr. Victor Vaughn and received his M.D. degree from the Medical School in 1905. In 1907, after service at the Lakeside Hospital in Cleveland, he went to Pasadena to become associated with Dr. James McBride, Director of Las Encinas Sanitarium (then known as the Southern California Sanitarium). When Dr. McBride retired in 1909 Dr. Smith assumed full control of the institution.

Although he was trained in internal medicine, he saw early in his career at Las Encinas that there was a deep and very close relationship between functional disorders of the psyche and many physical illnesses. He found too often that only by the solution of all the problems relating to the patient, emotional as well as physical, could a lasting cure be effected. In short, he practiced that phase of medicine now termed psychosomatic long before it was recognized as such.

Dr. Smith pursued this course with great success but in time felt that the developments in the study of psychiatry had become so great that they outstripped his fundamental knowledge of this new field of medicine. In his efforts to provide more complete and competent treatment to all aspects of internal medicine he realized that psychiatry held a prominent part in the program and he therefore allied himself with specialists in that field in order that the patient might be treated as a whole being, mind as well as body.

His interest in the human ailments led him further along the path devoted to the efforts of medicine to prolong the life of the individual. Soon he was giving much of his time to the treatment of the aged and to the diseases peculiar to that group. Here again, he began these activities long before the practice of geriatrics was viewed as a clinical specialty.

Dr. Smith was elected a Fellow of the American College of Physicians in 1924, and was certified by the American Board of Internal Medicine in 1937.

Dr. Stephen Smith is remembered not only by his many patients for his firm and thoughtful treatment, guidance and advice in their difficulties, but also by his colleagues to whom he afforded an institution for the treatment of various chronic and acute diseases, unique in its type.

CHARLES W. THOMPSON, M.D., F.A.C.P.

DR. GEORGE WADE WILSON

George Wade Wilson, M.D., F.A.C.P., formerly of St. Louis, Mo., died on June 6, 1947, in California, where he had resided and practiced for a number of years.

Dr. Wilson was born in St. Louis in 1891. He attended St. Louis University from which he received the degrees of Bachelor of Arts in 1910, Master of Arts in 1913, and Doctor of Medicine in 1914. Following internship in the Providence Hospital, Washington, D. C., Dr. Wilson became affiliated with the staffs of the Jewish, Barnes, and Missouri Pacific Hospitals in St. Louis. His academic and research appointments were Assistant in Medicine and Pathology, St. Louis University School of Medicine, 1916–17; Fellow and Assistant in Pathology and Bacteriology, Rockefeller Institute for Medical Research, 1917–19; Professor and Head of Department of Pathology, Bacteriology, and Preventive Medicine, Loyola University School of Medicine, 1919–20; Associate in Medicine, Washington University School of Medicine, 1920–24. Following his removal to the Coast, Dr. Wilson became affiliated with the University of Southern California School of Medicine, in which he held the title of Associate Professor of Clinical Medicine.

Dr. Wilson was elected a Fellow of the American College of Physicians in 1923.

DR. WILLIAM PEPPER

Dr. William Pepper, Dean Emeritus of the University of Pennsylvania School of Medicine, died December 3, 1947, at the age of 73.

Dr. Pepper retired two years ago after serving as Dean of the Medical School for 33 years. His death was attributed to coronary thrombosis. He was the third William Pepper to serve the University of Pennsylvania in a distinguished position. His grandfather held the chair of theory and practice of medicine from 1860 to 1864, and his father was provost and professor of medicine from 1881 to 1894. Dr. Pepper was a cousin of the former U. S. Senator George Wharton Pepper and a direct descendant of Benjamin Franklin. He held the degrees of A.B., M.D., and D.Sc., from the University of Pennsylvania and an honorary doctorate of laws from Temple University. He contributed many articles to leading medical journals and was a member of many scientific societies and a former President of the Association of American Medical Colleges. He was also a trustee of the University of Pennsylvania. He is survived by two sons, William Pepper, Jr., an officer of the Philadelphia Free Library, D. Sergeant Pepper, M.D., F.A.C.P., Assistant Medical Director of the Provident Mutual Life Insurance Company, a daughter, Mrs. Mary Pepper Parker, and a brother, O. H. Perry Pepper, M.D., M.A.C.P., Professor of Medicine in the University of Pennsylvania.

All of the many who knew Dean Pepper will recall the sympathetic and good humored interest with which those who consulted him were received, and the absolute integrity which even the most casual acquaintance perceived in him. His long and distinguished career covered a vital period of transition in medical education. In his passing American medicine has lost one of its links with the past.

DR. BENJAMIN JAFFEE BIRK

Benjamin Jaffee Birk, M.D., F.A.C.P., was born in Michigan City, Ind., on August 17, 1894. He received his B.S. degree from the University of Indiana in 1916 and his M.D. degree from Rush Medical College in 1919. He then served internships in the Michael Reese and Cook County Hospitals, Chicago. He did postgraduate work at the University of Chicago School of Medicine, and furthered his studies in internal medicine at the University of Vienna in 1927–28.

As a Milwaukee physician for almost thirty years, Dr. Birk served as Chief Resident, Chief of Staff, Head of Division of Medicine, and finally Head of the Department of Internal Medicine of Mt. Sinai Hospital. From 1940 to 1942 he was an Instructor of Internal Medicine in the Marquette University School of Medicine.

During World War I Dr. Birk served in the Army Medical Corps. He was commissioned in the Army of the United States again in 1942 as a lieutenant-colonel. Before going overseas he was chief of medicine at Fort Sheridan, Ill., after which he was attached to the Chinese Combat Command of the United States Army for thirteen months. In 1944, he was awarded the Legion of Merit with oak leaf cluster for especially meritorious conduct. He was discharged in 1946 with rank of colonel.

Dr. Birk was a member of the Military Order of World Wars, Association of Military Surgeons of the United States, Wisconsin Military Association, Reserve Officers Association, American Medical Association, Wisconsin Heart Association, American Heart Association, Milwaukee Academy of Medicine, Milwaukee County and Wisconsin Medical Societies. He had been a Fellow of the American College of Physicians since 1939.

KARVER L. PUESTOW, M.D., F.A.C.P.,
Governor for Wisconsin

DR. PAUL JAMES CONNOR

With the death of Dr. Paul James Connor of Denver, Colorado has lost one of its most active and capable internists. Dr. Connor was born in Madisonville, Texas, in 1887. He attended the Agricultural and Mechanical College of Texas before entering the University of Texas School of Medicine, from which he graduated in 1912. He came to Colorado from the Ancon Hospital, Canal Zone, in 1920. He was active on the staffs of the Presbyterian, St. Luke's and Mercy Hospitals, of Denver.

A diplomate of the American Board of Internal Medicine, Dr. Connor was particularly interested in endocrinology. He was also very active in the public health work of Colorado, and was President of the State Board of Health in 1931.

He was a member of the Denver City and County and Colorado State Medical Societies, the Inter-State Post Graduate Medical Association of North America, the American Association for the Study of Goiter, the American Diabetes Association, the Association for the Study of Internal Secretions and was a Fellow of the American Medical Association. Dr. Connor had been a Fellow of the American College of Physicians since 1931.

WARD DARLEY, JR., M.D., F.A.C.P.,
Governor for Colorado

DR. HENRY CLAY LONG

Dr. Henry Clay Long, one of Tennessee's well-known medical consultants, died at his home in Knoxville, September 14, 1947.

Dr. Long was born in Marion County, Tenn., October 15, 1878. He attended Pryor Institute and then received his M.D. from Vanderbilt in 1914. His ability as a student is amply shown by his election as a member of the honorary medical society, Alpha Omega Alpha.

His postgraduate study was at the Riverside and Bellevue Hospitals, New York, N. Y., and the New York Post-Graduate Medical School and Hospital. He was a diplomate of the American Board of Internal Medicine.

Dr. Long served in the Army in World War I.

He was a past president of the Knoxville Academy of Medicine, and a Member of the East Tennessee Medical Society, the Tennessee State Medical Society, and the Southern Medical Association. Dr. Long had been a Fellow of the American College of Physicians since 1936.

Dr. Long was a hard worker, a thorough student, and a conscientious physician.

WILLIAM C. CHANEY, M.D., F.A.C.P.,
Governor for Tennessee

DR. SAMUEL EDGAR MUNSON

Samuel E. Munson, M.D., F.A.C.P., dean of the medical profession of Springfield, Ill., died on October 2, 1947, at the Memorial Hospital there at the age of 81, following a long illness. He is survived by his wife and by his daughter, Miss Mary Munson.

Born in 1866 on a farm in Mechanisburg Township, Sangamon County, Ill., Samuel E. Muson was the son of Joel M. and Elizabeth Van Hook Munson, who had come to the state from Kentucky in 1857. Following three years of study at Valparaiso (Ind.) University, he taught school for three years and began meanwhile the study of medicine with the late Dr. George M. Kreider. He subsequently entered the Northwestern University Medical School and received the M.D. degree in 1893. After several years of practice in Mount Pulaski, he married Miss Daisy North of Rochester, Ill., and went with her to Europe where he attended various clinics in Vienna and studied at the University of Göttingen where, incidentally, his daughter was born. Upon returning to this country, he entered upon his practice of medicine in Springfield, Ill., which continued until a few months before his death. He was a member of the staff of the Springfield Hospital since 1900, and was president of the staff in 1910. From 1936 to 1941 he served as a member of the Medical Advisory Board of the Department of Health of the State of Illinois. In June of 1943, a dinner was held at Springfield in his honor, to mark his completion of fifty years in the practice of medicine, a distinction to which only 290 of the 12,500 physicians in Illinois had then attained. Dr. Munson was a diplomate of the American Board of Internal Medicine.

Dr. Munson received numerous recognitions for his professional work. He was a member and past president of the Illinois State, Central District, and Sangamon County Medical Societies; a member of the Mississippi Valley Medical Society; a Fellow of the American Medical Association. He was also a prominent member of the community as a member of the First Christian Church, as a 32nd degree Mason, past Commander of the Knights Templar; and as member of the Kiwanis Club.

Dr. Munson became a Fellow of the American College of Physicians in 1922. He rendered distinguished service to the College as Governor for Southern Illinois from 1923 to 1941. He was elected Third Vice President of the College for the year 1941–42.

Dr. Munson was held in great esteem by the members of his profession and all who knew him or of him. A skilled physician, he was very highly regarded for his sincerity and modesty and his deep interest in the young physician who sought his advice when getting started in the practice of medicine. His high ethical standards in life and in the practice of medicine deepen the loss of his passing to his family and the community.

CECIL M. JACK, M.D., F.A.C.P.,
Governor for Southern Illinois

DR. OLIVER WILLIAM WELCH

Oliver William Welch, A.B., M.D., M.P.H., F.A.C.P., Fairfield, Ala., died suddenly in Birmingham, Ala., on October 21, 1947, at the age of 40.

Dr. Welch was born September, 19, 1907, at Talladega, Alabama. He received his pre-medical education at the University of Alabama, and graduated from the Harvard Medical School in 1933. He did postgraduate work at the Boston City Hospital, Massachusetts General Hospital, and the Harvard School of Public Health, where he received his Master's Degree in Public Health in June, 1936. He then served as Associate Medical Officer in charge of Industrial Hygiene for the Tennessee Valley Authority until August, 1938, when he became permanently associated with the Department of Medicine of the Employees' Hospital, Tennessee Coal, Iron and Railroad Company, Fairfield, Ala. He was Chief of the Medical Service of this hospital at the time of his death. He had served overseas for two years during World War II.

Dr. Welch was a member of the Jefferson County Medical Association and of the Medical Association of the State of Alabama, and a Fellow of the American Medical Association. A diplomate of the American Board of Internal Medicine, he was elected to Fellowship in the American College of Physicians in April, 1947.

Dr. Welch was a keen clinician. He will be missed by his associates and his community.

E. Dice Lineberry, M.D., F.A.C.P.,
Governor for Alabama